THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1936

ORIGINAL ARTICLES.

THE SIGNIFICANCE OF NORMAL AND MORBID FORMATION AND DISTRIBUTION OF CELLULAR AND NON-CELLULAR CONSTITUENTS OF BLOOD AND LYMPH.*

By John L. Yates, M.D.,

DIRECTOR OF CANCER INVESTIGATION, MILWAUKEE COUNTY HOSPITAL, MILWAUKEE, WISC.

The identical objectives of medical workers, whatever be their laboratory and clinical endeavors, are to acquire and to apply knowledge needed to improve, devise and to utilize therapeutic methods that will minimize disabilities and thus prolong active life. Objectives can be attained by assisting people to develop, conserve and transmit to offspring the capacity to produce life-sustaining, health-maintaining and health-regaining groups of functions. Means to attainment are indicated through realization that the efficacy of each group of these fundamental functions depends upon production, equable and economic distribution of an adequate volume of blood and lymph of requisite quality.

Consequently, the methods assuring the utmost efficacy in prevention and treatment of antigenic and non-antigenic diseases are ultimately disclosed by hemology, which includes hemo-lympho-plasmology and hemo-lympho-cytology; *i. e.*, the structure, functions and modes of production and storage of each non-cellular and cellular constituent of blood and lymph and knowledge of activities responsible for wholesome and unwholesome modes of distribution of blood and lymph. Information needed to select and adroitly to utilize appropriate measures is derived from all sources—personal and

* Address of Chairman, Section of Abdominal and General Surgery, American Medical Association, Atlantic City, N. J., June 12, 1935.

family history, every manner of examination, clinical experience, etc., which will not be here discussed—but more particularly from normal and morbid physiology.

Normal physiology has shown that blood and lymph form the internal environment of a body (Bernard) which is separated from tissues by endothelial lining of cardiovascular walls. Balance in, among (Bernard, 1869) and between (Hewson, 1774) the cellular and non-cellular constituents of blood and lymph, together with balance (equity) in the distribution thereof, is requisite to health. The cellular and non-cellular constituents of the internal environment fluctuate qualitatively and quantitatively with alterations in living conditions and the total volume of blood in more or less active circulation, volumes distributed to divers structures at varying velocities and expenditures of cardiac energy likewise fluctuate with living conditions. Healthful balance in, among and between constituents, balance in total and unit volumes of blood and an economic distribution are conserved by automatic adjustments (Cannon). Automatic adjustments are pressor and depressor influences that so regulate hemopoietic and cardiovascular activities as to restrain fluctuations in formation and delivery of internal environment within upper and lower healthful limits. Consequently, all balances fluctuate between high (favorable) and low (unfavorable) limits, and life-sustaining functions produced when balances are favorable have a wider margin of safety, when balances are unfavorable, a narrower margin of safety. The duration of production of life-sustaining functions depends upon the inherent competence of hemopoietic cells, cardiovascular cells and the cells effecting automatic adjustments and upon the exertion-rest intervals of their experiences.

Morbid physiology has disclosed an almost incessant subjection of individuals to actions of pathogenic influences from conception until death. Unchecked pathogenic influences first reduce favorable to unfavorable balance in production or in distribution of constituents of blood and lymph, or both, then convert an unfavorable balance that is incompatible with disease into an imbalance that is incompatible with health and finally increase the imbalance until it becomes incompatible with life. Pathogenic influences awaken additional automatic adjustments (resistance, defense and repair) which tend to check them. If these adjustments are more or less effective they conserve favorable or unfavorable balances (health-maintaining functions); if ineffective for shorter or longer intervals and then become effective, they convert imbalance (disease) into balance (health-regaining functions); if persistently less ineffective, they protract; if more ineffective, they fail to protract production of life-sustaining functions.

Antigenic influences, exerted from establishment of a fetal circulation until death, are the entrance into internal environment from

tissue or from external environment (maternal circulation in fetus) or irritating cellular constituents and viruses (parasites) or non-cellular constituents (foreign proteins; *i. e.*, parasitic and non-parasitic antigens) which are, despite filtration by vascular endothelium, lymph glands, lungs, liver, spleen, bone marrow and kidneys, rapidly disseminated in some measure throughout the body. Automatic adjustments aroused by antigenic influences are local, intermediate and systemic responses. Local responses are evoked by irritation of tissue into which parasites are primarily implanted and in which antigens are primarily diffused. Intermediate responses are caused by irritation of vascular endothelium through which parasites and antigens pass into lymph and blood, the divers lymph and blood filters through which the lymph and blood flow and the vascular endothelium through which parasites and antigens pass from the lymph and blood to enter vascular walls and perivascular tissues. Systemic responses are occasioned by irritation of tissues by parasites and antigens that have passed into them through vascular walls. Automatic adjustments produce and introduce into the internal environment counterirritating cellular (increased leukocytes) and non-cellular (antibody) constituents which are rapidly disseminated and delivered through vascular walls into tissues containing parasites and antigens. If these adjustments are effective, they inactivate or destroy parasites and neutralize antigens promptly (health-maintaining functions) or after an interval of illness (health-regaining functions). If less ineffective, they protract, if more ineffective, fail to protract, production of life-sustaining functions. A continuous presence of antigens in and the repeated entrance of parasites into the internal environment necessitates an equally continuous formation of increased numbers of appropriate forms of leukocytes and an elaboration of antibodies. Thus the divers cells productive of health-maintaining and health-regaining functions requisite to survival are kept, so long as not incapacitated, in the state of active preparedness required to provide resistance and defense against the inevitably recurring more or less potent antigenic irritations.

Hemopoietic and cardiovascular cells and those productive of automatic adjustments (pressor and depressor nerve impulses, hormones, etc.) inherit strength or weakness and are beset from conception until death with non-antigenic influences; namely, the wear of usual, the tear of unusual modes of living, actions of non-antigenic irritants, etc., which, together with antigenic influences, determine the duration of cellular competence. Incompetence of these groups of cells to which antigenic influences may contribute can introduce fluctuations in their activities that exceed upper and lower healthful limits; *e. g.*, polycytoses or cytopenias, hyper- or hypoglycemia, hyper- or hypothyroxinemia, mental and nervous instability, inequable (Raynaud's) and uneconomic (hypertension)

distribution of unit and gross volumes of blood. Automatic adjustments aroused by non-antigenic influences consist of compensatory and adaptive alterations in structure and function of some cells to offset subcompetence in others. If the adjustments are immediately effective, they conserve balance (health-maintaining functions); if later they become effective, they restore balance (health-regaining functions); if persistently less ineffective, they protract, if more ineffective, fail to protract production of life-sustaining functions. The wear of usual modes, the restricted stress of less unusal modes of living and of milder irritations provide exercise whereby all but frail cells acquire strength so that non-antigenic influences tend to conserve and to raise the competence of cells productive of life-sustaining, health-maintaining and health-regaining functions. Antigenic influences can introduce non-antigenic diseases and *vice versa*, so combinations of both forms of disease are not infrequent.

Means to attainment of therapeutic objectives through coördinated laboratory and clinical efforts are indicated by normal and morbid physiology and experience. They are to establish hemologic data from repeated detailed examinations of the constituents of the internal environment and of the modes of their distribution and *to interpret these data in conjunction with all other information.*

The requisite data will answer the following questions:

Is there balance or imbalance in either blood and lymph formation or circulation, or both?

Prevention. Is any balance revealed by mean level of inevitable fluctuations favorable or unfavorable? If a balance is favorable, what measures will conserve it and thus continue insusceptibility by protecting the competence of cells productive of life-sustaining, health-maintaining and health-regaining functions? If a balance is unfavorable, is it regressing, stationary or progressing? Is reduction from favorable to unfavorable balance attributable to actions of antigenic, non-antigenic influences or both? How can pathogenic influences be eliminated without imposing additional handicaps? If an unfavorable balance is regressing, how can the person be assisted to regain and maintain a favorable balance? If stationary, how can regression be introduced and promoted? If progressing, how can an increasing unfavorable balance be arrested before it has exceeded healthful limits (susceptibility), regression be introduced and promoted? Repeated examinations furnish data that will determine whether the measures as they are being employed are efficacious or inefficacious, how they should be modified, how long they should be continued and when they should be reintroduced.

Treatment. Is the mean level of any imbalance high or low, acute or chronic, regressing, stationary or progressing? Is an imbalance attributable to actions of antigenic, non-antigenic or to both influences and how can pathogenic influences be eliminated

or reduced without adding more than transiently and immaterially, if at all, to existing burdens? If an imbalance is regressing, how can an individual be assisted to regain balance (recovery), to reëstablish (acquired insusceptibility) and to maintain a favorable balance (acquired immunity)? If stationary, how can regression of an imbalance be inaugurated and facilitated? If progressing, how can an imbalance be arrested before it has exceeded recoverable or viable limits and regression be introduced and fostered? Repeated examinations will furnish data that will indicate the efficacy or inefficacy of measures as they are being employed, suggest modifications or other methods, the duration of beneficial employment and when reëmployment will obviate recrudescence.

We must recognize our obligations to assist people to acquire and to conserve favorable balances or to regain and to maintain the most favorable or least unfavorable balances or imbalances circumstances permit. Satisfaction of those obligations demands not only the timely utilization of appropriate non-operative and also frequently of operative measures of established efficacy, but also the extension of this effort as information increases. It is not pertinent here to try to summarize actual and potential accomplishments with available knowledge and measures nor to attempt to suggest lines of endeavor that would widen the scope of accomplishments. If we realize that immunologic part of morbid physiology defines means to combat antigenic influences and morbid physiology discloses methods to combat non-antigenic influences, we can find dependable therapeutic indications from limited knowledge of and investigative indications from ignorance of (1) cellular; (2) non-cellular; (3) both cellular and non-cellular constituents; (4) the distribution of (5) and storage of both with provision of margins of safety.

1. What are the numbers and functions in health and disease of each variety of corpuscle and of platelets and what are the favorable and unfavorable influences that govern their production? What is the competence of these corpuscles and of the cells producing them as revealed by numbers and by proportions of immature, mature and senile forms? What are the inter-relationships shown by monocyte-lymphocyte, large lymphocyte-small lymphocyte, monocyte-neutrophil, eosinophil-neutrophil, and basophil-neutrophil ratios? Do the numbers, proportions and ratios indicate a favorable balance, an approaching or existing imbalance? What is the existing degree of competence or grade of incompetence of hemocytoblasts and how can their welfare be best served according as an active pathogenic influence be antigenic or non-antigenic? (Hemology has been dominated overlong by hemocytology, indeed by hemocytomorphology, just as pathology has been subjected to the benumbing influence of morbid anatomy. Valuable as is knowledge of alterations in numbers, proportion and ratios of corpuscles,

there are other alterations in the entire blood that are too frequently ignored and often furnish even more significant information.)

2. What is the volume of each constituent of blood plasma and lymph (water, proteins, carbohydrates, electrolytes, vitamins, hormones, chemical intermediaries in transmission of nerve impulses, anabolic and catabolic products, antigens, antibodies, etc.)? What are the relationships or ratios between the constituents; *e. g.*, water and solids, albumins and globulins, divers salts, carbohydrates, vitamins, fats and pressor and depressor hormones and intermediaries of nerve impulses, antigens and antibodies, etc.? Do the volumes, physicochemical attributes and ratios indicate a favorable balance, an approaching or existing imbalance? What is the competence or incompetence of cells producing non-cellular constituents? How can those cells be protected or their rehabilitation be promoted if the pathogenic influences are antigenic or non-antigenic? (Great as has been the advance in knowledge of the constituents of lymph and plasma, it is little more than introductory.)

3. What is the concentration of the plasma? Does it provide the wholesome degree of viscosity (normal sedimentation rate) requisite to appropriate distribution with optimum expenditure of cardiac effort? Is concentration of plasma raised (retarded sedimentation rate) or lowered (accelerated sedimentation rate)? Is sedimentation unduly retarded because of disproportionate increase in corpuscles (polycythemia vera)? Is it healthfully retarded by an unusual surplus of antibodies effecting a favorable balance in antigen-antibody ratio? Is sedimentation unduly hastened because an excess of antigenic irritants unneutralized by antibodies or a surplus of non-antigenic irritants present in the plasma have effected a withdrawal of water from tissues to dilute them and promote their elimination? (Hastened sedimentation caused by excess of unneutralized bacterial antigens was noted by Hewson, in 1774, as an increased buffy coat on surface of blood clots after phlebotomy. Accelerated sedimentation if provoked by presence of non-parasitic foreign proteins in plasma can be estimated as urticaria develops. Francis D. Murphy has observed the development of hastened sedimentation with rise of N.P.N. because of acute nephritis and of slowing of sedimentation as renal lesions subside. Obstructive jaundice introduces an irritating excess of bile salts into blood and hastens sedimentation. Hemolytic jaundice does not introduce such irritation and sedimentation is not accelerated, may even be retarded.)

4. Is equable distribution in healthful states associated with homogeneous mixture of constituents of plasma and homogeneous distribution of corpuscles in plasma whether circulation is more or less rapid? When there is inflammation, are appropriate leukocytes drawn to the periphery of the plasma in smaller vessels as a first

stage in migration by chemotropism of antigenic and non-antigenic (fibrin) irritants in the tissues? Are platelets similarly drawn to the periphery of plasma in vascular injury or inflammation? What cardiovascular and vasomotor states conserve and disturb the homogeneity of mixture and the usual proportions of all constituents of internal environment? Are such anomalies the cause or consequence of inequable distribution and if so, how are they correctable? Is arteriolar constriction the ultimate cause of essential hypertension? Does the constriction affect all arterioles or is it sometimes more pronounced in splanchnic vessels, sometimes in the systemic? If this explains why divers methods of treatment are dissimilarly efficacious, how can the distribution of constriction be recognized? (Efforts now being made to correct inequable and uneconomic distribution will eventually disclose the causes and establish prophylaxis.)

5. What are the extravascular and intravascular sites of storage for surplus cellular and non-cellular constituents? What influences regulate the storage of surplus constituents and withdrawals from storage of constituents needed to preserve balances? How can margins of safety be protected against shortages? When should potential shortages be prevented or actual shortages be covered by intravenous introduction of unmodified whole blood or of certain constituents; *e. g.*, salt, sugar? (Antibodies, because some forms of parasitic or non-parasitic antigens are ever present in tissues and in internal environment, are quite the most potent single contribution to health-maintaining and regaining functions upon which survival depends. All cells are repeatedly subjected to actions of antigens, virtually all cells elaborate antibodies, particularly the reticuloendothelium in lymph and blood filters. Surplus antibodies are distributed in lymph and blood and stored in tissues most liable to invasion by parasites, to infiltration by antigens (*e. g.*, skin and subcutaneous fat, mucosæ and submucosæ, serosæ and subserosæ, fascia delimitating regions and vascular endothelium) and in tissues harboring parasites. So long as antigen-antibody balance obtains, the numbers, proportions and ratios of leukocytes and the rates of sedimentation are wholesome *unless otherwise altered*. An excess of parasitic or of non-parasitic antigens in the internal environment effects almost immediate alterations in numbers and ratios of leukocytes and accelerates sedimentation. Recognition of these anomalies, if slight, may be difficult, but they usually are unmistakable and with other information are diagnostic and prognostic. This proof of the deficits in antibodies, likely the storage thereof, indicates the nature of aid to be given (*e. g.*, immune sera, ordinary and immunotransfusions of unmodified blood, glucose, etc.) if any be needed to protect or to hasten rehabilitation of the blood-forming and distributing structures.)

Summary. Formation and distribution of the constituents of blood and lymph are the fundamental functions of the living wherein every cell of a body participates.

Hemology; *i.e.*, hemo-lympho-cytology, hemo-lympho-plasmology and knowledge of the activities providing circulation and storage of the constituents of blood and lymph is consequently the basis of medical effort.

Qualitative and quantitative fluctuations in the constituents of blood and lymph, fluctuations in the total and unit volumes, in velocities, destination, storage and withdrawals from storage and utilization of proportions of blood and lymph are concurrent with changing living conditions.

Restrictions of fluctuations within wholesome limits maintains balances which are requisite to health.

Early recognition and interpretation of untoward alterations in constituents or in their distribution and storage reveal approaching or incipient disease (imbalance) indicate the antigenic or non-antigenic provocative influences and the most propitious preventive or corrective measures.

Repetition of examinations will establish the efficacy or inefficacy of measures *while they are being employed* by disclosing a reduction or an increment in untoward alterations and thus revealing progress toward or away from restoration and conservation of favorable balance upon which enduring recovery depends.

Additional knowledge is required to recognize lesser untoward alterations and wider experience to interpret them with dependable accuracy.

An appreciation of normal and morbid physiology that supplements hemology is requisite to progressive medical education and practice and to the investigations conducted in clinic and laboratory that will provide additional information imperatively needed.

HEMOLYTIC ANEMIA IN CARCINOMATOSIS OF THE BONE MARROW.

By Theo. R. Waugh, M.D.,
ASSISTANT PROFESSOR OF PATHOLOGY, MC GILL UNIVERSITY, MONTREAL, CANADA.

(From the Department of Hematopathology, Pathological Institute, McGill University, Prof. Horst Oertel, Director.)

It is a well recognized fact that profound changes often take place in the blood of persons suffering from malignant tumors. Far too frequently these are dismissed quite readily by the clinician on the basis of cachexia, without any effort being made to arrive at a satisfactory explanation. Such an attitude is as deplorable as the

once frequent use of the term "secondary" to designate all anemias which were not of the Addison-Biermer type. While there are exceptions, it is undoubtedly true that in the vast majority of cases of malignancy, one is able by careful study to arrive at a quite logical and satisfactory explanation of the hematopoietic disturbance.

If an attempt is made to analyze the causes of alteration in the morphologic blood picture in individuals with malignant growths (and by this we refer especially to cancer), one can find a very natural division into what might be called primary and secondary causes. Primary causes play a rôle when the abnormality of hematopoietic activity is brought about directly through the cancer cells themselves or chemical substances arising from them, that is their metabolic or excretory products. On the other hand, among the secondary causes we group those disturbances which result from the effect which the tumor growth exerts on other parts of the body and hence indirectly on the blood forming organs.

Before going on to a discussion of the changes in the blood due to the primary causes, it might be well to take up those resulting from secondary causes, as these are much more common and the mechanism of production for the most part is more obvious. These explain many of the changes which are frequently attributed to cachexia.

In a great many cases examination of the blood reveals a typically posthemorrhagic anemia. This is particularly the case in tumors of the stomach, large bowel, rectum and uterus. Persistent hemorrhages may occur from growths in these locations. Many times this loss of blood is not recognized until a very grave anemia results. Frequently in cases of carcinoma of the stomach with their accompanying achlorhydria, superficial examination of the blood has led to a diagnosis of pernicious anemia. This is in the vast majority of cases not a true pernicious anemia, but simply the result of a persistent blood loss, and careful examination shows that the blood findings lack all of the pathognomonic features of Addison's anemia. The cells are small with low hemoglobin concentration and if nucleated reds are present they are of the normoblastic or macroblastic type, in contrast to the megaloblastic forms of pernicious anemia. Moreover, there is not the reduction of myeloid white blood cells nor the thrombocytopenia and bilirubinemia of pernicious anemia.

Very rarely there do occur, however, cases of carcinoma of the stomach with the characteristic blood findings of pernicious anemia. We have one such in our records in which after a typical and rapid improvement in the anemia following liver therapy, the diagnosis of malignancy was confirmed by operation and histologic examination of the stomach. Whether these cases are to be interpreted as extraordinary combinations of the two conditions or whether the carcinoma plays a rôle in the production of the pernicious anemia,

is at present uncertain. In the light of our present knowledge it seems quite reasonable to presume that extensive malignancy in this organ might so disturb its functional activity as to lead to the particular changes necessary for the production of this specific form of anemia. On the other hand, it is extraordinary that the complication does not occur much oftener than careful analysis of the blood reveals.

In contrast to these cases showing posthemorrhagic anemias which really explain many of the anemias associated with cancer, we not infrequently encounter cases showing an increase in the number of red blood cells over the normal. These result for the most part from two main causes. First, in cases where, as for instance, in carcinoma of the esophagus the fluid intake is reduced and an anhydremia results, due to its quantitative reduction. In these cases we have a type of pseudopolycythemia and they may be readily recognized by the very high refraction index of the blood plasma. A second cause for increase in the red blood cells is anoxemia resulting from tumors of the thorax which interfere with the proper aëration of the blood. In these a true polycythemia, though of symptomatic type, results and figures well over 6,000,000 red cells per c.mm. may occur.

Turning more particularly to the changes in the white cells of the blood, it is very frequent in malignant tumors to find a leukocytosis. Differential examination shows as a rule an increase in myeloid cells, particularly the neutrophils and monocytes. The neutrophil forms often show more or less immaturity, that is a shift to the left, and frequently a comparatively large number of myelocytes. The eosinophils may or may not be increased and very often the lymphocytes are reduced. Many of these changes in the white cells are readily explained on the basis of inflammatory reactions which often accompany the tumor growth; while in those cases in which the blood loss has occurred the leukocytosis very likely, in part at least, is due to associated leukopoietic activity of the bone marrow.

Eosinophilia seems more particularly to occur in cases of lung involvement and may bear some relation to the associated bronchiectasis. The platelets of the blood are quite frequently numerous and it is rare, except in the more extraordinary pictures resulting from primary causes which we shall discuss later, to find any thrombocytopenia.

A hemorrhagic diathesis, however, may result from secondary causes in cases of obstruction to the bile ducts with jaundice and here it is interesting to note that the severity of the hemorrhagic condition seems to stand in more intimate relation to the length of time which jaundice has existed than to its severity. This suggests that it is not so much the jaundice as associated dysfunction of the liver parenchyma which lies at the basis of the prolonged bleeding.

In many cases of malignant growths the color of the blood plasma is not changed and there is no marked bilirubinemia. However, where obstruction to the bile channels, as mentioned above, occurs, a high bilirubinemia results with the typical van den Bergh findings of obstructive jaundice. Chemical examination of the plasma, in rapidly spreading growths, shows relatively early an increase in globulin and a decrease in the albumin proteins. This wou d appear to be one of the principal causes of the rapid sedimentation velocity and quite likely results from the destruction of tissue which occurs.

Returning now to the primary causes of changes in the blood in malignant tumors, we are treading for the most part on theoretical ground. Under this category we have to include changes which are directly referable to the presence of the cancer cells themselves in the hematopoietic organs, or changes which they effect in the blood cells through metabolic or chemical products liberated by them. Many of these anemic conditions in cancer are dismissed rather cursorily on the basis of "cachetic" changes; but if one attempts to analyze them more carefully, it is found comparatively difficult to derive from this phrase any satisfying explanation. The question naturally arises first, whether "malignant" cells more particularly cancer cells, phagocytose the red blood cells in sufficient numbers to produce an anemic state. In our experience this seems very doubtful. It is not uncommon to find iron pigment in cancerous tissue, but on the other hand many times it is absent and its presence seems to depend upon and be in direct proportion to the amount of hemorrhagic extravasation of blood in the tissues. Pigment is liberated in these extravasated areas, but it is doubtful if any appreciable phagocytosis of the erythrocytes by the cancer cells occurs.

It has been recognized for some time that in certain, though not all, cases of extensive metastases of cancer in the bone marrow, profound changes may take place in the blood. These consist of the presence of a large number of nucleated red cells, even though the anemia may not be severe. In addition myelocytes and even myeloblasts may be thrown into the circulation. In fact, these changes have been looked upon by hematologists for some time as suggestive, in certain cases, of metastatic carcinoma of bone. They generally have been explained on the basis of irritative effects on the myeloid tissue caused by the presence of the neoplastic cells. The fact that some cases of very extensive and diffuse metastases in the bone marrow may run their course without these blood changes has led to the general belief that the influence exerted by the cancer cells is not a mechanical disturbance, but rather due to "toxic" effects exerted by the cells upon the neighboring proliferating myeloid tissue. Why this effect should take place in some cases and not in others has not been explained. Moreover, it has been observed, particularly in cases of metastatic carcinoma of

bone with anemia, that the anemia was of hyperchromic type with high color index. By this we do not mean that the blood picture was in any way diagnostic of pernicious anemia, but rather that a macrocytic anemia with a preservation of high hemoglobin concentration was found.

Another change which has occasionally been reported in cases of generalized carcinomatosis is the presence of a considerable amount of hemosiderosis in the liver and spleen. This has been explained on the basis of "toxic" effects from the cancer cells leading to hemolysis of the erythrocytes in the vicinity, the pigment then being borne by the blood stream and stored in the reticulocyte of the spleen and liver. While such a theory is inviting, it is rather difficult to substantiate it.

It is quite obvious, therefore, from this review of our knowledge of blood changes in carcinoma, that those arising from secondary causes seem well established and their explanation is fundamentally sound, but that the changes attributed to primary causes remain indefinite and are covered by that common cloak of ignorance, the term "toxin," which is itself unsatisfactory in the final analysis.

It seems, therefore, worthwhile to record detailed and complete blood studies on two of these cases which seem to enable us to form a somewhat clearer conception of the basis and mechanism of the effect of some of these primary causes. These findings would seem to correlate and bring together into a more reasonable explanation some of these blood disturbances.

Case Reports. Case 1.—The case which first brought this to our attention was that of a traffice officer, aged 58, who entered the hospital September 25 complaining of loss of weight, loss of appetite and general rundown condition for the past 6 months, aching pains in the legs for 6 months, impaired vision, diplopia, vomiting after meals, ringing in the ears and impaired hearing on the right side for 4 months.

The patient had enjoyed exceptionally fine health until the onset of the present illness 6 months previous to admission. At that time he had what he believed to be an attack of grippe with development of pain in both legs. Since then he had never felt well. About 2 weeks after the onset he lost his appetite and his weight dropped from 225 to 153 pounds. His vision gradually failed and recently his family noticed a prominence of his left eye and swelling about it.

Physical examination showed temperature and respirations normal, with pulse 94. His general appearance was that of a very emaciated man of stated age, slightly lethargic but intelligent and coöperative. His skin and mucous membranes were very pale. There was a definite swelling in the left temporal region causing protrusion of the left eye. The liver was palpable 4 cm. below the costal margin and a small hard mass could be felt to the right and above the umbilicus. The spleen was not palpable. The inguinal glands were hard and immovable and considerably enlarged. Rectal examination showed the prostate to be fixed and very hard with obliteration of the median furrow and induration extending into the adjacent structures.

Laboratory examination showed the urine to be acid with a faint trace of albumin and specific gravity 1.012. The Wassermann reaction was

negative. Roentgen ray examination of the lumbar vertebræ, pelvis, ribs and scapulæ showed sclerosing bone changes suggestive of secondary carcinoma. There was no evidence of metastases in the lungs. The body of the twelfth dorsal was collapsed. The skull was negative.

Morphologic Blood Examination. Red blood cells, 1,900,000; white blood cells, 3000; hemoglobin, 35% (5.46 gm. per 100 cc.); color index, 0.92; red blood cells stain well. Marked anisocytosis and poikilocytosis. Moderate polychromatophilia. No punctate basophilia or nucleated reds. Reticulated reds, 6%; fragility, markedly increased; corpuscle volume, 16%; averaged corpuscle volume, 84 cu. μ; Hemoglobin concentration, 0.97; sedimentation velocity, very rapid.

White blood cells (400 examined):

	%	Per c.mm.
Neutrophils	61.25	1837
Eosinophils	2.0	60
Mast cells	0.25	8
Monocytes	4.5	135
Lymphocytes	32.0	960

Reduction in all forms, particularly myeloid elements.

Platelets, 86,000; irregular in size and shape.

Bleeding time normal. Coagulation: fibrin, 3 min.; congealing, 6 min.; with calcium, 6 min.; retraction present.

Plasma, pale yellow with greenish tinge. Refraction, 49.

Van den Bergh: Direct: prompt, negative; delayed, positive; indirect: 2 units bilirubin.

Microscopic Fragility Test:

	Unhemolized +000	%
Tube 100	1500	100.0
70	1020	68.0
65	800	53.0
60	540	36.0
55	140	9.3
50	40	2.7
45	0	0.0
40	0	0.0
35	0	0.0
30	0	0.0

The morphologic blood picture shows striking changes which point distinctly to a severe hemolytic type of anemia with interference with bone marrow activity. The hemolytic character of the anemic condition is shown by the number of reticulated red cells, the markedly increased fragility of the erythrocytes, the bilirubinemia with a delayed, positive, direct van den Bergh reaction and the preservation of a high hemoglobin concentration.

The general myelophthisic character of the blood picture is indicated by the marked reduction in myeloid white cells, the thrombocytopenia and the lack of nucleated reds.

It seems fairly certain, therefore, that this blood picture is the result of a combination of two factors: (1) a hemolytic process and (2) a general interference with myeloid activity.

Unfortunately this patient was discharged from the hospital immediately following the blood examination and before the results had been received and the extraordinary character of the case realized. Efforts to bring about a readmission were unsuccessful, and even more disappointing was the fact that we were unable to obtain an autopsy at the time of his death, approximately 3 months later.

Although no biopsy was performed, there seemed little doubt the patient was suffering from a primary carcinoma of the prostate with extensive metastases in the osseous system.

At this time we did not realize the possible significance of the severe hemolytic type of anemia and were inclined to attribute the combination of extensive carcinomatosis and this form of anemia to an extraordinary coincidence.

Somewhat later, however, a second case came to our attention which, in a great many respects, was similar to the first, and this impressed upon us the fact that we were dealing in both cases not with a coincident but rather with an associated and extraordinary form of reaction on the part of the hematopoietic system in generalized carcinoma of bone. Fortunately in the second case we were able to carry out a thorough clinical examination followed by autopsy findings.

CASE 2.—This case was that of a housewife, aged 49, who entered the Royal Victoria Hospital June 10, complaining of pain in the back and legs, weakness, dyspnea and palpitation. One year previous she had had the right breast removed at another hospital. The pathologist reported a rapidly growing carcinoma situated immediately beneath the nipple, without evidence of invasion of the deeper tissues or axillary glands. She remained in good health to within 3 months of the present admission, when the pain and weakness first appeared.

Physical examination showed a sallow color with slight cyanosis, no glandular enlargement or palpable masses, a purpuric rash over the chest, abdomen and lower back, the spleen enlarged down to the umbilicus and very firm, and the liver just palpable. Temperature, 100° F.; pulse, 110; respirations, 25.

Laboratory examinations showed the urine to be free of Bence-Jones protein, free acid of gastric contents 10° and total acid 20°, stools dark in color with no occult blood, and the Wassermann reaction negative. Roentgen ray of the osseous system failed to show any rarefaction of the bones, but dark shadows were present in the lungs, suggestive of metastases.

Morphologic Blood Examination. Red blood cells, 2,300,000; white blood cells, 8300; hemoglobin, 41% (6.4 gm. per 100 cc.); color index, 0.9; red blood cells: cells on average small, but stain well. Few macrocytes. Marked anisocytosis, slight poikilocytosis and polychromatophilia. No punctate basophilia. Twenty-two nucleated reds in 300 white blood cells, as follows: 3 orthochromatic and 13 polychromatic normoblasts; 3 polychromatic and 3 basochromatic macroblasts. Corpuscle volume, 18%. Average corpuscle volume, 78 cu. μ. Hemoglobin concentration, 1; reticulated reds, 8%; fragility, markedly increased.

White Blood Cells (300 examined):

	%	Per c.mm.
Neutrophils	44.6	3702
Metamyelocytes	4.0	332
Oxy. myelocytes	12.6	1046
Neutrophilic myelocytes	6.6	548
Eosinophils	2.0	166
Mast cells	1.6	133
Monocytes	8.3	689
Lymphocytes	20.3	1684

Many immature and perverted myeloid forms.

Platelets: 26,000; scarce, but normal size and shape. Bleeding time moderately prolonged. Coagulation: fibrin time, rapid; congealing time,

prolonged (20 minutes); calcium time, prolonged; retraction slow but marked.

Plasma, dark yellow with marked greenish tinge. Van den Bergh: direct: prompt, negative; delayed: strongly positive; indirect: strongly positive, 6 units bilirubin.

The blood picture is that of a hemolytic anemia with other extraordinary features.

The erythrocytes show an increased fragility with a considerable number of reticulocytes. They tend to preserve a good hemoglobin concentration, as is the rule in hemolytic conditions. In addition there is a considerable number of nucleated red cells in various stages of development. Some of these are macroblastic forms.

The leukocytosis is only slight, but there is a distinct tendency for immature and perverted myeloid forms to enter the circulation. The reduction in platelets is marked and with this goes the prolonged bleeding time and alteration of the coagulation time met with in other thrombocytopenic conditions. The bilirubinemia completes the picture.

Here again the blood picture is: (1) a profound hemolytic anemia and (2) myelophthisic changes with thrombocytopenia and hemorrhagic diathesis.

The patient rapidly declined and died on June 30. Autopsy showed extensive metastasis of the breast carcinoma in the lungs, liver, bone marrow and cervical and mediastinal lymph nodes.

The neoplastic areas in the bone marrow were extraordinary in that they consisted for the most part of emboli of tumor cells, definitely within vascular channels. These cells had apparently proliferated there, dilating and distorting the walls, but only occasionally was there evidence of actual spread and growth among the myeloid elements. This did occur, however, with the formation of accompanying fibrous stroma. The result of this high degree of vascular embolization was a profound circulatory disturbance, without appreciable actual displacement of functioning bone marrow elements by the neoplastic cells. Extensive hemorrhagic extravasations had occurred about the tumor plugs into the myeloid tissue, and in these disintegration of erythrocytes was obviously taking place.

No positive evidence of phagocytosis of the red blood cells or their cell detritus by the cancer cells could, however, be demonstrated. In some areas the extravasation of blood into the marrow reached a mild degree of infarction. There was no granular pigment, and stains for iron were negative. In areas where the myeloid tissue was best preserved it was found to be actively erythropoietic with numerous erythroblasts in various stages of development. It was also very hemorrhagic.

The spleen weighed 780 gm., was firm and the cut surface hemorrhagic. Histologic sections showed a large amount of blood in the pulp, considerable myeloid metaplasia and many large phagocytic cells containing granules of pigment, which gave a positive reaction for iron (hemosiderin). The parenchymal cells of the liver also showed a large amount of similar pigment. No pigment, however, was present in large cancer areas elsewhere in the body.

Discussion. There seems no reason to doubt but what in this second case we are again dealing with a hemolytic anemia in generalized carcinomatosis. It is, of course, possible that both these cases represent simple coincidents. However, it is difficult to explain them on this ground, and it seems much more reasonable to believe that the diffuse carcinomatosis involving the marrow is a distinct etiologic factor in the production of the hemolytic condition.

The histologic studies carried out on the bone marrow show extensive plugging of the larger vascular channels by the cancer cells which has led to the formation of extensive hemorrhagic extravasations. In some of these areas the extravasated blood remains free, while in others there is distinct evidence that it has undergone coagulation with the formation of fibrin and fusion and disintegration of the red cells. It is a well established fact that such extravasated blood undergoes hemolysis with the formation and deposition of hemosiderin, which might be taken by some as a satisfactory explanation of the hemolytic anemia. To our minds, however, such an explanation is not satisfactory. In the first place, it does not explain the increased fragility of the circulating erythrocytes nor does it explain the changes in the spleen, such as the engorgement by blood of the pulp with compression of the venous sinuses—a picture quite characteristic of hemolytic jaundice.

We are, therefore, rather of the opinion that there may occur in the body, as a result of extensive carcinomatosis of bone, a generalized alteration in hematopoietic activity, which is of such a nature as to lead to the changes necessary for the production of a typical hemolytic anemia. Moreover, it is possible that the explanation of this phenomenon may lie in extensive embolization of the vascular channels of the myeloid tissue by tumor plugs with consequent profound circulatory disturbances and hemorrhagic extravasations.

Whether the alteration in the fragility of the erythrocytes to hypotonic salt solution, which was present in both cases, is of primary importance in the pathogenesis of the anemia or only a secondary phenomenon, is difficult to decide. Unfortunately studies were not carried out on the diameters of the red blood cells, so we are unable to state whether the shift to a smaller but thicker, *i. e.*, spherical, type of erythrocyte occurs here, as we have been able to demonstrate in other forms of anemia with increased fragility. However, it seems to us a very interesting point, if our conclusions are correct, that we have in these cases an example of a hemolytic anemia in which the primary etiologic factor is apparently definitely known, although the mechanism of production still remains in doubt.

Moreover, as regards the incidence of metastases in the bones, there is no question but what a great many cases of tumor-spread, in which even Roentgen ray examination may fail to show evidence of metastases, nevertheless eventually disclose extensive involvement of the osseous system. The frequency of metastatic involvement of bones by malignant tumors is much higher than is generally supposed, as was recently shown by Schmorl. By careful examination, both grossly and histologically, of the vertebral column, he was able to demonstrate the presence of metastases in 66% of all cancers of the prostate, 33% of primary cancers of the bronchi, 33% of bladder cancers and 40.7% of all sarcomata. Moreover, in similar examinations carried out on 500 autopsies of cases of malignant tumors of

various parts of the body, he was able to demonstrate vertebral metastases in 19.6% of the men and 15% of the women. These figures are most interesting, and certainly show the incidence of metastases in the bones to be much higher than has been previously believed. Undoubtedly many cases have gone unrecognized, where thorough studies of the bones were not carried out.

Summary. Therefore, two facts confront us: first, that by a thorough and detailed examination of the blood we are able to demonstrate in certain cases of "malignant" growths a hemolytic form of anemia, which in the presence of more superficial examination would likely be passed over as merely secondary or explained on the basis of cachexia; and second, that a more detailed and systematic examination of the bones in cases of these tumors reveals an extraordinarily high percentage of metastases in the osseous system.

In the light of this evidence, therefore, we cannot but feel that a more thorough study in the directions indicated would possibly establish this phenomenon as not too uncommon a cause of the severe anemias in the presence of "malignant" growths. It seems, therefore, advisable to continue these investigations, and it is for the purpose of inviting these that this fragmentary report is offered.

REFERENCES.

Copeland, M. M.: Skeletal Metastases, Arising from Carcinoma and from Sarcoma, Arch. Surg., **23**, 581, 1931.

Cosin, L.: Pseudo-myelomatous Carcinomatosis, Brit. Surg., **23**, 110, 1935.

Faulds, J. S., and Mackay, W.: A Case of Cancer of the Pancreas, with Metastases in Bone Marrow and Liver, and Megaloblastic Anemia, Lancet, **2**, 1334, 1927.

Geschickter, C. F., and Copeland, M. M.: Tumours of Bone, Am. J. Cancer, New York, 1931.

Grawitz, P.: Ueber maligne Osteomyelitis und sarkomatose Erkrankungen des Knochensystems als Befunde bei Fallen von pernicioser Anämie, Virch. Arch., **76**, 353, 1879.

Harrington, A. W., and Kennedy, A. M.: Bone-marrow Metastases and Anæmia in Gastric Cancer, Lancet, **1**, 378, 1913.

Harrington, A. W., and Teacher, J. H.: Case of Carcinoma of the Stomach with Metastases in the Bone Marrow, and a Blood Picture Suggestive of Pernicious Anæmia, Medicine, **73**, 241, 1910.

Houston, T.: The Conditions that Simulate Pernicious Anæmia, Brit. Med., **2**, 1257, 1903.

Mach, R. S., and Klages, F.: Les anemies cancereuses myelogenes, Presse méd., **38**, 831, 1930.

Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1931.

Piney, A.: Blood Changes Associated with Metastatic Tumours of Bone, Brit. Surg., **11**, 707, 1923.

Piney, A.: Carcinoma of the Bone Marrow, Ibid., **10**, 235, 1922.

Piney, A.: Metastases in Bone Marrow, Brit. Path. and Bacteriol., **25**, 140, 1922.

Schmorl, G., and Junghanns, H.: Die gesunde und kranke Wirbelsaule im Röntgenbild, Leipzig, Georg Thieme, 1932.

Seemann, G., and Krasnopolski, A.: Akute "Leukanämie" mit starker extramedullaren Blutbildung als Folge ausgedehnter Knochenmarksverdrangung durch Magenkrebsmetastasen, Virch. Arch., **262**, 697, 1926.

Weil, P. E., and Clerc, A.: La spléno mégalie chronique avec anémie et réaction myéloide du sang, Semaine méd., **22**, 373, 1902.

Willis, R. A.: The Spread of Tumours in the Human Body, London, Churchill, 1934.

Zadek, I., and Sonnenfeld, A.: Das klinische und hämatologische Krankheitsbild der metastatischen Knochengeschwulste, Klin. Wchnschr., **9**, 2245, 1930.

BACTERIOPHAGE SERVICE TO PATIENTS WITH STAPHYLOCOCCUS SEPTICEMIA.*

By Ward J. MacNeal, M.D.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL,

AND

Frances C. Frisbee, A.B.,
ASSOCIATE IN BACTERIOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL, NEW YORK CITY.

(From the Department of Pathology and Bacteriology, Columbia University.)

Scope. In 1932 we presented a report[1] on the bacteriophage treatment of 15 patients with staphylococcus bacteremia. Since that time a few additional cases have been presented in the papers from our laboratory but there has been no published analysis of a series of consecutive observations. Now we have records of 163 patients with staphylococcus septicemia for whom we have rendered bacteriophage service. We have chosen, however, to limit the present discussion to the 100 consecutive cases immediately following in time the 15 reported in 1932, namely Patients 16 to 115. Some of the more general features will be presented in this present paper and the more intimate study of the 100 patients will follow in the next paper.

Consideration of the nature of bacteriophages, their sources, technique of propagation, titration, testing and packaging for clinical use will be omitted from this paper. We purpose here to consider the practical application of these lytic agents in the treatment of septicemia. This in itself is a research problem worthy of careful study.

Diagnosis. The diagnosis of staphylococcus infection and bacteremia requires some discussion. For our purpose, and for practical clinical work also, in our opinion, only the positive blood culture or evidence of metastatic localization of staphylococcus infection can be accepted as adequate proof of staphylococcus bacteremia and of these the blood culture occupies first position. The blood culture should be made in such a way as to yield the most convincing evidence. We ordinarily draw the blood from the elbow vein into citrated saline solution in a Taylor[2] tube, avoiding any contact with the outside air. Coagulation is prevented by mixing the blood with the citrate. Measured portions are then added to melted agar to produce a smooth mixture of agar and blood and plated before the medium becomes solid. Measured portions of the citrated blood

* These studies have been aided by a grant from the Josiah Macy, Jr., Foundation.

are also transferred to bottles of broth, some of which may be covered with sterile oil if desired, although this is unnecessary for growth of the staphylococcus. After the agar is solid all the cultures are placed at 37° C. Growth of the staphylococcus can often be recognized within 24 hours, nearly always after 2 days and very exceptionally the colonies may be first found on the fourth day. A count of the colonies affords an approximate measure of the number of viable bacteria per cc. of blood and comparison of the plates and broth cultures affords evidence of the reliability of the entire procedure. The positive blood culture is the point of departure for preparation of the specific bacteriophage for the patient and under no circumstances should these plates and bottles be prematurely destroyed.

Staphylococcus infection which has not yet invaded the blood stream may be recognized sometimes by experienced observers on the basis of clinical evidence, as for example in a furuncle, but, in general, a bacteriologic examination of exudate from the local lesion is necessary for accurate diagnosis. The early specific etiologic diagnosis of such local lesions may permit the proper early treatment to forestall a bacteremia. Once the infection of the blood stream has become established the local lesion becomes subordinate in importance, a fact sometimes not fully appreciated by the less experienced surgeon. At the moment we are not especially concerned in dicussing such local lesions, although local application of bacteriophage may be helpful.

Therapeutic Technique for Septicemia. After the diagnosis of staphylococcus bacteremia has been established we have recommended the immediate use of our stock bacteriophage and at the same time the prompt preparation of a specific phage. This specific phage is prepared by subjecting a culture of the organism from the patient's blood to lysis by a mixture of stock phages. The filtrate of this lyzed culture contains a potent bacteriophage adapted to the specific organism as well as specific bacterial proteins. The preparation of this specific phage, including adequate sterility tests, may require 2 to 8 days. During this interval of waiting, the stock phage is employed in therapy.

When there are recognizable local lesions we apply copious amounts of broth phage to the open surfaces and inject through a fine needle (gauge 27) the asparagin phage into the lymph spaces all about the lesion. These injections are repeated every 24 to 48 hours and the local applications are made at each dressing. Chief reliance, however, is placed upon the intravenous injections of the asparagin bacteriophage. Once the bacteremia is recognized we prefer to postpone operative procedures and transfusions for at least 24 hours and during this time, the intravenous bacteriophage

injections are pushed to produce a shock reaction. Evidence of serious cardiac or pulmonary disease is reason for greater caution but even here we try to cause a "reaction."

The injections are made through a fine needle (gauge 27) and great care is exercised to avoid permanent injury to the vein. Ordinarily one makes the entire series of injections into the same site without extravasation or thrombosis. We like the flat tourniquet[3] of garter elastic, as it permits accurate adjustment of pressure, easy release by one hand and is less annoying to the patient than a cylindrical tourniquet. We prefer, when possible, to keep away from the elbow veins, reserving these for transfusions and avoiding any responsibility for their destruction by the phage injections. Veins on the hands, forearms, feet, ankles and neck may be used to advantage. To preserve the vein one removes the tourniquet before beginning the injection and applies pressure over the puncture in the vein *immediately* upon withdrawing the needle, maintaining an adequate even pressure here for a full five minutes. This is best done by applying the tourniquet to hold the compression pad. Leaving this after-care of the vein to an uninstructed nurse often results in extravasation of blood. Elevation of the part and rest from movement are helpful. While we shall not cite specific examples, there are in our series instances in which intravenous therapy was discontinued because of technical difficulty in keeping the veins in good condition during the many injections required.

We begin with a small intravenous dose, ordinarily 0.5 cc. but sometimes with as much as 2 cc. if the colony count in the blood is above 50 per cc. The doses are spaced at approximately 45 minutes and are increased in arithmetic progression 0.5–1–2–3–4–5–6–7–8–9–10 cc. and then continued as 10 cc. doses until about 100 cc. total amount has been administered. Then one increases to 15–20–25 or even 30 cc. at one injection. If a shock occurs at any time during the series the injections are discontinued for 8 to 20 hours or until the next morning. If shock does not occur the prognosis is not so good. Therefore we like to persist, but it is probably wise to stop at a total of 100 cc. in children under 5 years, 200 cc. in those under 15 years and 300 cc. in older persons, even if no reaction appears. In such cases one makes a renewed attempt to shock the patient on the third or fourth day or as soon as a specific phage is ready. Rectal temperature is recorded every hour while the series of injections is being given.

When there is reason for greater haste the doses may be increased more rapidly in series, as for example, 1–2–4–8–12–16–20–25–30 cc. This saves the doctor's time but is probably more dangerous for the patient with enfeebled circulation or pulmonary involvement.

The shock reaction may be forecast by a slight rise in temperature. Often, however, it begins without warning by complaint of feeling cold, pallor and cyanosis of extremities and of face, chattering of the teeth and general and highly distressing rigor. We ordinarily apply external heat, administer oxygen by nasal catheter, give adrenalin and rarely morphin. Having warned the patient in advance that we expect to produce a chill we now attempt to reassure him and the anxious family by expressions of satisfaction that the chill has come. Serious immediate danger appears to be confined to patients with soft endocardial vegetations which may be dislodged during this reaction. After shaking for 5 to 70 minutes the temperature is ordinarily between 104 and 107° F. Then the patient suddenly ceases to shake. He becomes rosy and breaks out in profuse perspiration. The temperature falls rapidly in an hour and by the next morning may be below 99 or even below 98. After the chill ceases the patient ordinarily feels at peace with the world and usually goes to sleep and remains quiet for several hours.

On the day when such a series of doses is given the patient should not be subjected to transfusion nor to surgical incision, because these may confuse the clinical picture. Saline solution may be given intravenously if desired.

For 2 or 3 days after the shock reaction the patient is given smaller doses, morning and evening. Ordinarily the dose employed is approximately ½ the last dose of the series which was followed by the shock reaction. For example if, on the first day, the patient had received at intervals doses of 1–2–3–4 cc. and then developed a chill, we give on the following day an intravenous dose of 2 cc. in the morning and again in the evening and continue the same doses for 2 or 3 days. On these days transfusion may be given and easily accessible purulent collections may be drained. If the blood culture remains positive another attempt to shock the patient is undertaken on the fourth day and again on the seventh day. When the blood culture becomes negative we continue the small intravenous doses twice daily for a week or two, then once daily for about a month. When the patient is allowed to be out of bed we change to subcutaneous injections, 2 or 3 times a week, continuing these for 3 to 6 months. The treatment is varied to meet the particular situation and greatest attention is given to the results of blood cultures taken once or twice each week.

Temperature, pulse rate, blood pressure and body weight are carefully recorded and frequent physical examination is not neglected. The urine is examined frequently. Infarction of the kidneys is very common in staphylococcus bacteremia. In most instances these renal lesions heal with continued intravenous bacteriophage therapy.

A further consideration of the various complications and metastatic localizations of the infection will be omitted.

Examples of Success and Failure. Somewhat detailed records of patients who survived and of others who died have been presented in our earlier publications. Each patient presents an individual problem and it seems worth while to include here as examples the records of 2 patients of the present series, 1 who survived and 1 who succumbed.

CASE 1.—A. W. (*Patient No. 59*), male, aged 39, was admitted to the Post-Graduate Hospital on July 12, 1933 (Fig. 1). He had fallen ill 2 days before, with vague abdominal distress, weakness and fever. A blood culture taken at that time was positive and we identified *S. aureus*. Another blood culture taken after admission to the hospital (July 14) yielded the same organism and a third blood culture taken on July 16 was similar. Urine culture taken on July 17 remained negative. Bacteriophage therapy was requested on July 18 by the physician, Dr. A. W. Duryee, to whom we are indebted for the clinical record, and the bacteriophage treatment was given by us personally. On July 18 after taking a blood culture, an intravenous injection of 0.5 cc. stock asparagin staphylococcus bacteriophage was given in 2 minutes at 12.20 P.M. This was followed an hour later by 1 cc. intravenously. At 2.50 P.M. the patient had a slight chill; external heat was applied and his temperature rose to 100° F. At the time this did not seem to be a definite reaction to bacteriophage but, because the clinical condition of the patient seemed satisfactory, no more phage was given on that day. On subsequent days an intravenous dose of 0.5 cc. bacteriophage was given twice daily. On Saturday, July 22, an attempt was made to push the bacteriophage injections to a shock reaction. Signs of left pleurisy had been recognized on the previous day and the specific bacteriophage was ready for use. On July 22, a preliminary blood culture was taken at 8.50 A.M., and then at 9.04 A.M. an intravenous injection of 0.5 cc. of the specific phage was given. This was followed by 1 cc. at 9.47 A.M.; 2 cc. at 10.32 A.M.; 4 cc. at 11.22 A.M.; 8 cc. at 12.20 P.M.; 10 cc. at 1.25 P.M.; 10 cc. at 2.18 P.M.; 10 cc. at 3.19 P.M.; 12 cc. at 4.05 P.M. and 12 cc. at 4.50 P.M. The total amount for the day was 69.5 cc. The patient remained comfortable, without chill or any evident reaction although his temperature reached 102.4° at 6 P.M. At the time we were seriously disappointed at this failure to induce a shock but later, when it became evident that the infection of the blood stream had already disappeared, the failure to produce a shock seemed to be explained. Subsequently smaller doses of the specific phage were continued until the patient was discharged on August 9. The pleurisy and the infiltration of the left lung had entirely disappeared by this time and the patient left the hospital in good condition.

After discharge from the hospital, the patient continued to receive subcutaneous injections of bacteriophage once or twice a week. Apparently this treatment was discontinued some time in October or November. Early in December he developed a furuncle on the side of his neck and this was treated by us on December 10 and 12, with prompt relief. At this time the patient was urged to continue with the subcutaneous injections at the hands of his physician in order to forestall further activity of the infection. After a few weeks this was again discontinued.

On April 15, 1934, the patient was again admitted to the hospital with fever and tenderness over the right kidney. Cultures of the blood and of the urine were negative. Because of the previous history it seemed probable

that we had to deal with a septic infarct of the kidney. However, in the absence of more certain criteria, it was decided to explore the right kidney. Preceding the operation an intravenous injection of 2 cc. of his specific bacteriophage was given at 1.33 P.M. and the operation, begun at 3.36 and completed at 4.10 P.M., disclosed an abscess of the lower pole of the right

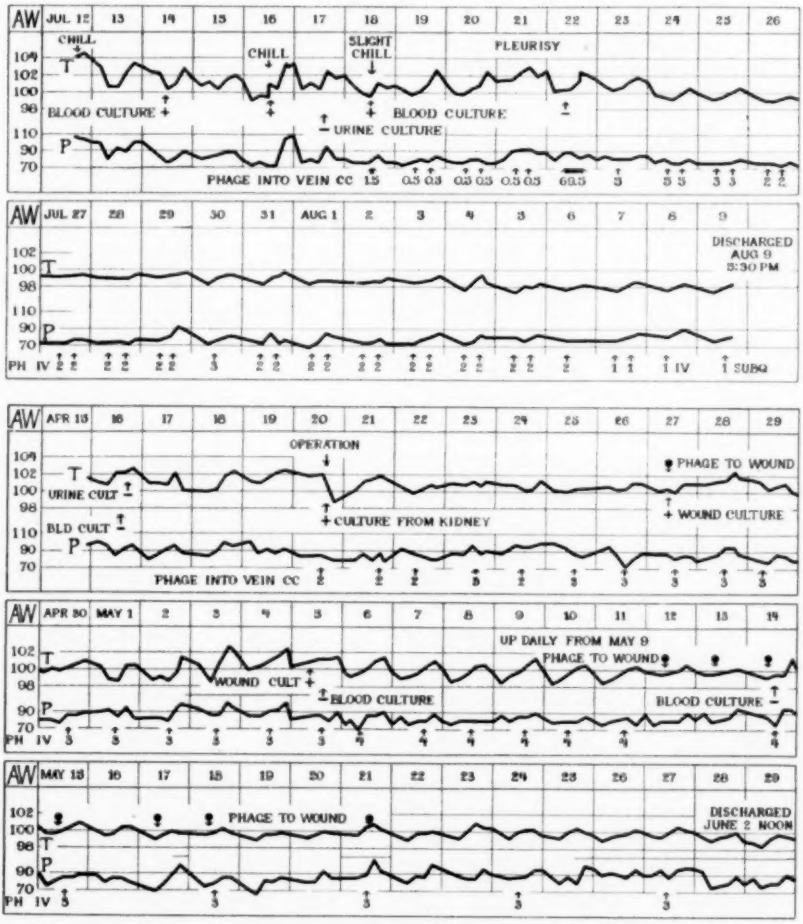
AW
JUL 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
CHILL
CHILL
SLIGHT CHILL
PLEURISY
BLOOD CULTURE
BLOOD CULTURE
URINE CULTURE
PHAGE INTO VEIN CC 1.5 0.5 0.5 0.5 0.5 0.5 0.5 6 0.5 5 5 5 3 3 2 2
JUL 27 28 29 30 31 AUG 1 2 3 4 5 6 7 8 9
DISCHARGED AUG 9 5:30 PM
PH IV 2 2 2 2 2 2 3 2 2 2 2 2 2 2 2 2 2 2 1 1 1 IV 1 SUBQ
APR 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29
OPERATION
PHAGE TO WOUND
URINE CULT
CULTURE FROM KIDNEY
WOUND CULTURE
BLD CULT
PHAGE INTO VEIN CC 2 2 2 5 2 3 3 3 3 5
APR 30 MAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14
UP DAILY FROM MAY 9
PHAGE TO WOUND
WOUND CULT
BLOOD CULTURE
BLOOD CULTURE
PH IV 3 3 3 3 3 3 4 4 4 4 4 4 4
MAY 13 16 17 18 19 20 21 22 23 24 25 26 27 28 29
PHAGE TO WOUND
DISCHARGED JUNE 2 NOON
PH IV 3 3 3 3 3

FIG. 1.—Abridged clinical record of A. W., male, aged 39, during two admissions to the hospital, namely July 12, 1933, to August 9, 1933, and April 15, 1934, to June 2, 1934.

kidney with a perinephritis. This was incised and drained. Cultures of the exudate gave a growth of *S. aureus*. The postoperative course was rather uneventful. Intravenous bacteriophage was given daily until May 11 and at intervals of 3 days thereafter until discharge from hospital on June 2. Subcutaneous injections of bacteriophage twice a week were continued thereafter for some months. The patient has remained well.

The record of this patient serves to illustrate some features of the bacteriophage therapy of staphylococcus sepsis which are now fairly well established. When the treatment is begun before there are destructive lesions in the vital organs, the outlook is better. If the infection of the blood stream is such that only a few colonies of staphylococcus develop in the blood culture, then the intravenous injection of a relatively small amount of bacteriophage will usually be sufficient to cause a chill. In this particular case the colonies were always less than 1 per cc. of blood and the blood culture taken on July 18, just before starting the bacteriophage injections, gave positive growth of *S. aureus* in only one broth flask and none on the plates. The patient chilled after only 2 intravenous doses, 0.5 and 1 cc., of bacteriophage. Subsequently, on July 22, when we again attempted to cause a chill reaction, the patient failed to react although a series of 10 injections, from 9.04 A.M. (0.5 cc.) to 4.50 P.M. (12 cc.) amounting to a total of 69.5 cc. bacteriophage, were given intravenously within 8 hours. On this date the blood culture taken just before the first injection of bacteriophage remained sterile. This result is in accord with our conception gained from other similar experiences, namely, that the typical shock reaction comes when the amount of bacteriophage injected has the proper quantitative relation to the bacteria in the blood stream. If the blood stream is sterile one may fail to produce a reaction even with large amounts of bacteriophage. Also when the blood stream is heavily infected or when massive collections of bacteria are directly in relation to the blood, as in vegetative endocarditis, one may have to administer very large amounts of bacteriophage before the patient reacts. We believe that the shock reaction is not due directly to substances contained in the bacteriophage itself but that it is brought about by an interaction, probably opsonic, between the bacteriophage and the accessible bacteria.

This record also illustrates the very common tendency for staphylococcus bacteremia to result in renal infarction. In our experiments on rabbits, kidney infarction has been very common and in our series of human septicemias it has been rather frequent. In the patients, the renal infection often heals without incision when adequate intravenous bacteriophage treatment is given.

The record of this patient also illustrates the danger of metastatic localization of the infection as a sequel to the bacteremia. It is true that not all patients fall victims to such later manifestations, but these late lesions have been common enough in our series for us always to recommend continuation of bacteriophage injections for a period of 3 months after apparent complete recovery from a blood stream infection with staphylococcus.

CASE 2.—As an example of unfortunate result we have chosen Y. R. (*Patient No. 90*), female, aged 6, under the care of Dr. W. D. Crecca of Newark, New Jersey, to whom we are indebted for the case record. She fell ill on Sunday, February 18, with a chill and general discomfort. On February 19 the left ankle was painful and the temperature ranged from 101° to 104°. Upon admission to the hospital on February 22 the temperature was 100°, pulse 120; a soft systolic blow was heard at the apex of the heart. There was swelling with fluctuation over the medial malleolus of left ankle. On February 22 at 11.38 A.M. pus was evacuated from the lower end of the left tibia and a plaster dressing applied. Blood culture taken on February 23 gave a growth recognized as *S. aureus* on February 24 and on this day bacteriophage was obtained from us by messenger. Beginning at 7 P.M. intravenous doses were given at intervals, 1–1–2–3–4–5–6–7 cc. stopping at 1 A.M., February 25. There was no evident reaction. About 8 A.M. February 25, the dressing was removed and 20 cc. bacteriophage was applied to the wound, and at 10 A.M. 4 cc. phage was given intravenously. The condition appeared very grave and Dr. Crecca asked us to see the patient and continue the bacteriotherapy. At 6.40 P.M. we took a blood culture and then began a new series of intravenous phage doses, 5 cc. at 6.45 P.M. ending with 22 cc. at 1 A.M., the total amount being 114 cc. There

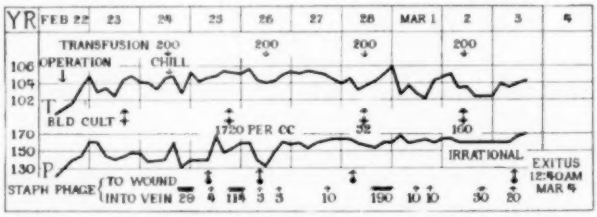

FIG. 2.—Abridged clinical record of Y. R., female, aged 6, during her treatment in hospital, February 22 to March 4, 1934.

was no reaction and the situation appeared hopeless. On the next day the rich growth in the blood culture was evident and the colony count after 48 hours' incubation of this blood culture taken on February 25 amounted to 1720 per cc. of blood. Smaller doses of phage were continued on February 26 and 27 and on February 28, because the patient was still alive and somewhat brighter, we were again called to Newark. The blood culture taken on February 28 yielded only 52 colonies per cc. In the afternoon and evening a total of 190 cc. of bacteriophage was given intravenously in divided doses between 3 P.M. and 11 P.M. without definite reaction, although there was perhaps a suggestion of reaction in the temperature rise to 106° at midnight and fall to 102.8° at 4 A.M. March 1. On March 1 we were somewhat encouraged by the lower colony count on the blood culture of February 28 and by the lower temperature of the patient. The pulse rate, however, remained high. Bacteriophage, 10 cc., was given twice on March 1. On this day extensive consolidation of the left lung was recognized and there was also evidence of meningeal irritation, but the cyanosis was less. On March 2 a blood culture was taken at 10 A.M. and a transfusion given. This blood culture later developed 160 colonies per cc. of blood. Bacteriophage was discontinued. In the evening, however, at the earnest insistence of the parents we were again called to continue the bacteriotherapy. At this time the pneumonia was very extensive, respirations 76 per minute, the patient was irrational with moderate rigidity of extremities and neck.

After 2 intravenous injections of 25 cc. each the injections were stopped. On March 3, however, another intravenous dose of 20 cc. phage was given at 10 A.M. and the wound was irrigated with phage. Death occurred at 12.40 A.M., March 4, with extensive pneumonia and terminal meningitis. Autopsy was not permitted so that the condition of the heart remains uncertain.

The record of this patient resembles that of several other children in our series, who were subjected to operation for osteomyelitis. When the infection of the blood stream is already established these children do not seem to withstand very well a bone operation under general anesthesia. On that account we now favor a more conservative program of intravenous bacteriophage therapy to overcome the septicemia before attacking the local lesion in the bone. However, each patient presents a special problem and judgment is difficult. Children with rheumatic or congenital defects of the heart are particularly handicapped in the fight against an infection of the blood stream even without the added burden of an anesthetic and surgical shock. The importance of the preliminary blood culture is evident.

At the present time we should not be satisfied to stop after a total dose of 29 cc. of intravenous bacteriophage in such a case. One should keep on trying to induce the shock reaction until the total dose has reached at least 100 cc., unless definite clinical contraindications become manifest.

The reduction in number of bacteria in the circulating blood from 1720 per cc. on February 25 to 52 per cc. on February 28 is noteworthy and it appears to have resulted from the bacteriophage treatment. We have not yet seen a recovery after the blood culture has revealed more than 250 colonies per cc. of blood. The observation in this case encourages one to believe that even such a high colony count may not be a certain indication of fatal outcome.

Summary. 1. The diagnosis of staphylococcus septicemia should be supported by positive blood culture made in such a way as to give reliable evidence of the approximate number of viable bacteria in the blood of the patient.

2. The technique of the bacteriophage therapy is described.

3. The shock reaction to intravenous bacteriophage appears to depend upon interaction between the bacteria, the bacteriophage and the natural defense mechanisms of the host.

4. An example of success and an example of failure are presented.

REFERENCES.

1. MacNeal, W. J., and Frisbee, F. C.: Bacteriophage as a Therapeutic Agent in Staphylococcus Bacteremia, J. Am. Med. Assn., **99**, 1150, 1932.

2. Taylor, R. M.: Apparatus and Technique for Taking Blood, Proc. New York Path. Soc., **14**, 37, 1914.

3. Straub, M. E., and MacNeal, H. P.: A Tourniquet for Intravenous Procedures, Arch. Derm. and Syph., **29**, 717, 1934.

ONE HUNDRED PATIENTS WITH STAPHYLOCOCCUS SEPTICEMIA RECEIVING BACTERIOPHAGE SERVICE.*

By Ward J. MacNeal, M.D.,
PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL,
AND
Frances C. Frisbee, A.B.,
ASSOCIATE IN BACTERIOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL, NEW YORK CITY.

(From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.)

The selection of the 100 patients for the present list has been made on the basis of objective criteria. First, there must have been received by us a request for bacteriophage service and therefore the series may be regarded as unselected. Second, there had to be reasonably convincing evidence that a blood stream infection with staphylococcus actually existed. In most instances there were repeated positive blood cultures and the organism was submitted to us for study. We have, however, included in the list several patients who died without a proper culture being submitted to us and a few patients have been included without acceptable evidence that a positive blood culture was ever obtained. When one considers that relatively few of these 100 patients were seen by us in person, it is noteworthy that decision as to admitting or excluding a patient from this list did not more frequently meet with serious difficulty. All patients who died have been included even if the evidence of staphylococcus sepsis seemed rather frail. We have stopped arbitrarily at Patient 115 in consecutive order, thus reserving for a later discussion the rapidly growing list of patients coming to our records after August 11, 1934. There were some patients whose records presented particular difficulty as will be evident in the later discussion.

Relation to Season of Year. Table 1 presents data of patients with staphylococcus bacteremia from No. 16 to No. 115 inclusive. At first glance one is struck by the fact that the period February 3 to August 8, 1932 has 12 recorded cases with no survivals. From August 9 to November 28, 1932, inclusive, there were, however, 5 recoveries in a series of 10 cases. This is followed by another period of discouraging experience from December 3, 1932 to June 2, 1933, inclusive, during which time 16 patients were given bacteriophage service for septicemia without any recoveries. Since June 3, 1933, every period of 2 months contains at least 1 successful case. Possibly this variation in mortality may have been related to the season of the year, to alterations in virulence of the disease or to a combination of fortuitous factors which are unrecognizable. During 1932

* These studies have been aided by a grant from the Josiah Macy, Jr., Foundation.

and 1933 more recoveries were observed in cases treated in the last half of the year as compared with the first half. In the first half year of 1932 we gave service to 10 patients without a recovery; in the corresponding portion of 1933 to 15 patients with 1 recovery and in the first half of 1934 to 23 patients with 5 recoveries, making a total of 42 deaths and 6 recoveries. On the other hand, for the period July 1 to December 31 in 1932, we served 15 patients with 5 recoveries; in 1933 in the second half 29 patients with 11 recoveries and in 1934 from July 1 to August 12 there were 8 patients with 3 recoveries, making totals of 33 deaths and 19 recoveries.

Other possibilities require consideration. We see in this record a challenge to close scrutiny of the technical methods employed in the preparation of the bacteriophage filtrates used in treatment and we are inclined to believe that these agents may have been more suitable at certain particular times. The stock bacteriophage has not been standardized and every effort is still being made to increase its efficacy in the light of continued experience.

TABLE 1.—DATA ON 100 CASES OF SEPTICEMIA RECEIVING BACTERIOPHAGE.

No.	Date.*	Patient.			Clinical conditions.	Operation.	Positive blood culture.	Death.
	1932							
16	Feb. 3	DC	M	24	Purulent arthritis of knee, septicemia	Feb. 5	Feb. 2	Feb. 15
17	Apr. 12	CW	M	36	Apr. 7, sepsis after hemorrhoidectomy	Mar. 28	Apr. 10	Aug. 8
18	May 3	JR	M	67	Apr. 19, gangrene left foot, diabetes	Apr. 26	Apr. 20	June 10
19	May 19	EH	M	35	May 17, furuncle of nose, extending	May 19	May 17	May 20
20	May 26	AZ	M	62	May 18, urinary infection	None	May 21	May 26
21	May 28	AC	M	61	May 7, furuncle on finger; May 21, chill	None	May	May 31
22	May 28	ML	F	48	May 24, severe chill of cryptic origin	None	May 26	May 29
23	May 30	FE	M	31	May 23, cryptogenic sepsis	None	May 30	May 31
24	June 8	KP	F	26	June 2, furuncle on face	June 6	June 6	June 11
25	June 22	FH	F	18	June 14, furuncle on arm; June 17, chill	None	June 20	June 23
26	July 26	EP	F	26	July 17, sepsis after childbirth, July 16	July 27	July 17	Aug. 4
27	July 31	EK	F	12	July 6, multiple furuncles; appendectomy	July 27	July 29	Aug. 17
28	Aug. 9	TO	M	25	July 7, nasal furuncle	July 14	July 21	Recovery
29	Aug. 9	LH	M	39	May 26, osteomyelitis of fibula	Many	Aug. 2	Sep. 9
30	Aug. 24	EH	F	15	Aug. 5, puncture wound of foot	Aug. 19	Aug. 21	Recovery
31	Sep. 23	LB	F	8	Sep. 18, pansinusitis; sepsis	Sep. 18	None	Oct. 5
32	Oct. 5	MU	M	21	Sep. 19, fracture of sternum; mediastinitis	Oct. 5	Oct. 6	Recovery
33	Oct. 17	BO	F	61	Oct. 1, sacral carbuncle; diabetes	None	Oct. 15	Oct. 19
34	Oct. 20	GT	F	47	Oct. 10, carbuncle; diabetes	Oct. 10	Oct. 14	Nov. 5
35	Nov. 10	HL	M	15	Oct. 7, osteomyelitis of femur	Oct. 16	Oct. 11	Recovery
36	Nov. 17	PS	M	16	Nov. 2, contusion of thorax; osteomyelitis	Nov. 16	Nov. 16	Nov. 17
37	Nov. 28	DM	F	11	Nov. 19, furuncle of face	None	Nov. 25	Recovery
38	Dec. 3	JB	F	47	Oct. 21, furuncle of nose; sepsis	Many	Oct. 28	Dec. 16
39	Dec. 22	LC	M	15	Dec. 13, osteomyelitis; epidural abscess	Dec. 14	Dec. 20	Jan. 1
40	Dec. 24	MI	F	12	Dec. 14, cryptogenic sepsis, tachycardia	None	Dec. 21	Dec. 28
	1933							
41	Jan. 20	MM	F	17	Jan. 17, extraction of tooth	Jan. 17	Jan. 18	Jan. 21
42	Jan. 20	MH	F	17	Dec. 23, osteomyelitis of ilium	Dec. 28	Jan. 19	May 1½
43	Jan. 24	FS	M	35	Dec. 22, fracture of skull base	Jan. 12	Jan. 5	Jan. 29
44	Jan. 24	VM	F	21	Dec. 31, cryptogenic fever	Jan. 23	Jan. 21	Jan. 24
45	Jan. 26	EC	F	11	Empyema; myocardial abscesses	Jan. 24	Jan. 24	Jan. 26
46	Feb. 9	MT	F	4	Feb. 2, osteomyelitis of foot	Feb. 6	Feb. 5	Feb. 9
47	Feb. 10	SR	M	71	Jan. 14, furuncles on back of neck	Feb. 7	Feb. 9	Feb. 15
48	Feb. 18	CO	F	16	Jan. 25, acute mastoiditis	Jan. 28	Feb. 3	Mar. 13
49	Apr. 4	GS	F	25	Mar. 26, abortion; sepsis	None	Apr. 2	Apr. 8
50	Apr. 4	JP	M	32	Feb. 28, furunculosis; pyemia	May 2	None	May 27

* This is the date when our bacteriophage service was requested in each respective case.

No.	Date.*	Patient.			Clinical conditions.	Operation.	Positive blood culture.	Death.
	1933							
51	May 3	AR	M	27	Old osteomyelitis; operation Apr. 28	Apr. 28	Apr. 29	May 4
52	May 20	NT	F	45	May 1, compound Colles' fracture	May 1	May 20	May 25
53	May 27	EK	M	57	May 18, carbuncle on forehead	None	May 27	May 29
54	June 3	HP	M	21	Apr. 22; sore throat and malaise	May 21	May 11	Recovery
55	June 17	SK	F	31	June 12, pustule on chin	None	June 16	June 17
56	July 1	AR	F	49	June 29, renal abscess	Many	June 29	Recovery
57	July 10	AN	M	57	June 9, abscess of left knee; osteitis	Yes	July 8	Oct. 8
58	July 15	HK	M	19	June 25, carbuncle on neck	June 25	July 11	July 16
59	July 18	AW	M	39	July 10, cryptogenic fever	None	July 12	Recovery
60	Aug. 3	JM	M	11	July 12, polyarthritis; heart murmur	None	July 21	Aug. 25
61	Aug. 7	HP	M	13	July 31, baseball injury to thigh	None	Aug. 4	Aug. 19
62	Aug. 21	LB	M	36	Leukemia and terminal sepsis	None	Aug. 19	Aug. 26
63	Aug. 26	GK	M	36	Aug. 2, infected finger; pyemia	Aug. 22	Aug. 24	Aug. 28
64	Aug. 31	HC	M	41	Aug. 25, meningitis; endocarditis	None	Aug. 28	Aug. 31
65	Sep. 2	DM	M	23	Aug. 5, carbuncle on forearm; pneumonia	None	Aug. 31	Recovery
66	Sep. 3	MC	F	8	Aug. 28, cellulitis of face	None	Aug. 29	Recovery
67	Sep. 13	LM	M	33	Sep. 5, osteomyelitis for 20 years	Sep. 11	Sep. 13	Sep. 16
68	Sep. 15	MP	F	25	Aug. 12, childbirth; Aug. 14, chill	None	Aug. 17	Recovery
69	Sep. 23	AM	M	37	Sep. 14, furuncle of nasal septum	None	Sep. 20	Sep. 23
70	Sep. 26	SG	M	21	Aug. 14, furunculosis	None	Sep. 14	Oct. 5
71	Oct. 10	TH	M	29	Sep. 21, compound fracture of ankle	Oct. 4	Oct. 6	Recovery
72	Oct. 28	LW	F	19	Oct. 16, purulent arthritis of hip	Oct. 26	Oct. 26	Oct. 31
73	Nov. 3	RS	F	31	Nov. 1, severe headache and fever	None	Nov. 1	Nov. 3
74	Nov. 13	FD	M	16	Nov. 10, fever of cryptic origin	Nov. 11	Nov. 10	Recovery
75	Nov. 14	CW	M	0	Ill since birth on Oct. 21	None	Nov. 11	Nov. 16
76	Nov. 14	RL	F	3	Oct. 23, pneumonia	None	Nov. 1	Recovery
77	Nov. 17	RW	M	5	Nov. 8, osteomyelitis of leg	Nov. 15	Nov. 15	Recovery
78	Nov. 25	FD	M	27	Nov. 9, cryptic fever with cough; empyema	None	Nov. 20	Recovery
79	Nov. 29	JK	M	8	Nov. 21, cryptic fever; appendectomy	Nov. 23	Nov. 27	Recovery
80	Nov. 30	RM	M	31	Nov. 22, furuncle of nose	None	Nov. 29	Dec. 1
81	Dec. 6	RJ	M	53	Mitral endocarditis since May	None	Sep. 10	June 4
82	Dec. 10	AK	M	40	Nov. 1, ruptured appendix	Nov. 1	Dec. 8	Dec. 12
83	Dec. 22	AE	F	6	Nov. 7, osteomyelitis of ilium	Nov. 17	Nov. 14	Dec. 31
84	Dec. 25	CT	F	14	Dec. 23; chills, fever; endocarditis	None	Dec. 25	Dec. 26
	1934							
85	Jan. 9	EO	F	24	Dec. 30, furuncle on face	Jan. 7	Jan. 6	Jan. 18
86	Jan. 24	VC	F	12	Jan. 16, fever blister on lip	None	Jan. 22	Jan. 26
87	Jan. 26	VH	F	12	Jan. 7, osteomyelitis of heel	Several	Jan. 15	June 20
88	Jan. 27	CB	M	64	Jan. 1, cryptogenic septicemia	None	Jan. 17	Recovery
89	Feb. 21	EM	M	28	Jan. 16, recurrent old osteomyelitis	Feb. 1	Feb. 17	Recovery
90	Feb. 24	YR	F	6	Feb. 18, cryptic fever; osteomyelitis	Feb. 22	Feb. 23	Mar. 4
91	Mar. 12	WL	M	66	Feb. 25, angina, cervical adenitis	Mar. 6	None	Mar. 14
92	Mar. 18	GB	F	38	Dec. 25, furunculosis, empyema	Mar. 5	Mar. 16	Mar. 22
93	Mar. 20	WJ	M	46	Mar. 1, nephrectomy; Mar. 22, thoracotomy	Mar. 1	Mar. 19	Mar. 23
94	Mar. 31	NG	F	44	Mar. 26, cryptogenic fever	None	Mar. 28	Apr. 1
95	Apr. 22	JB	M	26	Apr. 13, carbuncle of nose	Apr. 17	Apr. 19	Recovery
96	Apr. 24	GS	M	65	Apr. 18, furunculosis, stupor	Apr. 14	Apr. 18	Apr. 24
97	May 1	MW	M	40	Mar. 25, furuncle on neck, septicemia	None	Apr. 28	May 5
98	May 8	AJ	F	80	May 2, furuncle on face, diabetes	May 8	May 6	May 9
99	May 10	EB	F	15	Mar. 20, furuncle on face, pyemia	July 7	May 7	Recovery
100	May 13	MD	F	12	Mar. 26, otitis media; mastoidectomy	Apr. 13	May 10	Recovery
101	May 24	MT	F	10	May 7, furuncle on back; osteomyelitis	May 21	May 21	June 8
102	June 6	LS	M	34	Wound of thumb on Dec. 24	Dec. 24	Jan. 19	June 15
103	June 7	GB	M	0	May 25, a feeble infant; otitis media	None	June 4	June 8
104	June 11	AC	M	20	June 7, fulminating otitis media	June 5	June 10	June 13
105	June 20	CB	M	16	June 14, osteomyelitis after thumb wound	June 15	June 18	June 22
106	June 23	HM	M	19	Apr. 30, diabetes and sepsis	May 9	May 7	July 3
107	June 27	DD	F	10	June 24, osteomyelitis, endocarditis	June 24	June 24	July 24
108	July 3	KH	M	37	May 4, wound of thumb; sepsis	Yes	June 20	Recovery
109	July 6	DC	M	11	June 21, abdominal pain	None	June 30	July 14
110	July 18	WN	M	16	July 14, tooth extraction; sepsis	July 14	July 17	Recovery
111	July 28	SG	M	39	July 25, infected varicose veins	July 26	July 25	Aug. 2
112	July 30	EO	F	31	June 26, childbirth; June 28, chill	July 16	July 23	Recovery
113	Aug. 6	RM	M	15	Aug. 2, pain in thigh; osteomyelitis	Aug. 18	Aug. 4	Aug. 23
114	Aug. 11	TC	F	4	Aug. 4, cellulitis of foot	Aug. 8	....	Aug. 13
115	Aug. 12	NS	M	62	July 7, cystotomy; Aug. 7, prostatectomy	Aug. 7	Aug. 11	Aug. 15

* This is the date when our bacteriophage service was requested in each respective case.

Relation to Other Factors. Of far greater significance, however, are factors which do not appear at once in such a chronologic table. Among these may be mentioned age and sex of the patient, condition of the vital organs, such as heart, lungs, brain, kidneys, at the start of bacteriophage treatment, susceptibility of the infecting organism to bacteriophage lysis, virulence of the infection, delay in instituting treatment and wisdom exercised in carrying out the treatment.

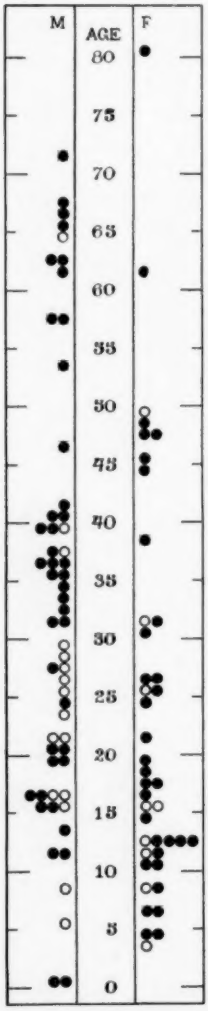

FIG. 1.—Distribution according to age and sex of 100 cases of staphylococcus septicemia. Hollow circles indicate survivals and solid black circles indicate deaths.

As to distribution according to sex and age (Fig. 1), there were 42 females and 58 males, an apparently insignificant difference. One boy was 15 days old and another 3 months old; 1 woman was 80 years old. Evidently no age is exempt from this disease. In the first decade of life there were 4 boys with 2 survivals and 7 girls with 2 survivals. In the second decade there were 12 boys with 3 survivals and 17 girls with 4 survivals. One therefore sees a suggestion that females under 20 years are more frequently afflicted than are the males of the first two decades of life. From ages 20 to 39, inclusive, however, the males greatly predominated in this series and that in spite of the occurrence of staphylococcus puerperal sepsis in the females. In the third decade there were 12 males with 8 survivals and 6 females with 1 survival, and in the fourth decade 15 males with 2 survivals and 4 females with 1 survival. Beyond age 40 there were 15 males, the oldest 71 years of age, and of these only 1, a man of 64 years, survived; while there were only 8 females over 40 with 1, aged 49, surviving. One gets the impression, which will require confirmation by larger figures, that patients under 30 years have a better prognosis and that the males between 15 and 30 years constitute the group with best chance for survival.

Susceptibility of the Staphylococcus to the Available Bacteriophages. In most instances the staphylococcus of sufficient virulence to invade the blood stream is found to be susceptible to lysis by our stock staphylococcus bacteriophage. There are, however, a few exceptions in this series. Somewhat resistant bacterial strains were encountered in Patients 62, 78, 81 and 106. Patient 62 was dying

of leukemia complicated by sepsis, and serial filtrations to enhance the lytic action of the phage were discontinued upon death of the patient. In the other 3 cases we succeeded in enhancing the lytic power to full potency by repeated filtration of cultures in series. In 2 instances, Patients 82 and 89, the culture submitted to us was found to be completely resistant to our stock bacteriophage and attempts to enhance the lytic activity were discontinued because further bacteriophage therapy was not desired. In 20 cases of the series we failed to receive a culture of the infecting organism in spite of repeated requests. In 74 cases the culture from the patient was found completely susceptible to our stock staphylococcus bacteriophage in the first trial. In general we have the impression that the staphylococcus resistant to bacteriophage is of relatively lower virulence than the phage-susceptible strains, but further observations are required before an unreserved statement can be made in regard to this point.

The Survivals. The surviving patients require particular consideration. There are 25 ranging in age from 3 years to 64 years.

Survivals. The youngest patient to recover, R. L., *No. 76*, a female, aged 3, was admitted to the Perth Amboy General Hospital on October 23, 1933, with diagnosis of pneumonia, second degree burn of the right chest wall and excoriation of buttocks. Blood cultures taken on November 1 and November 11 yielded *S. albus*. A total amount of 8 cc. of stock staphylococcus bacteriophage was given intravenously on November 14 and the injections were continued subsequently in small doses. On January 17, 1934, Dr. H. P. Fine reported a complete recovery.

A boy of 5, R. W., *No. 77*, was admitted to the Methodist Episcopal Hospital, Brooklyn, on November 12, 1933, with osteomyelitis of the leg which began with pain on November 8. The knee joint was opened on November 15 and pus evacuated. Blood culture taken on November 15 and again on November 17 yielded *S. aureus*. Stock staphylococcus bacteriophage was requested and used locally and intravenously from November 17 to November 21. On that day the specific preparation was ready and its daily use begun. After drainage of an abscess of the thigh on November 21 bacteriophage therapy was discontinued. Blood cultures were negative on November 23, 28, December 10 and 13. The femur was opened on December 6, and on January 5, 1934 the limb was sacrificed by thigh amputation. The patient was discharged March 11 and the wound was entirely healed on June 10, 1934.

M. C., *No. 66*, a girl of 8, was admitted to the Essex County (New Jersey) Hospital August 28, 1933, with furuncle and cellulitis of the face. Blood culture of August 29 gave a heavy growth of *S. aureus*. Blood cultures of August 31, September 2 and 4 were positive. On September 3, intravenous doses of stock staphylococcus bacteriophage to a total of 19 cc. were given, probably a series of 1–2–3–5–8 cc., followed by the usual shock reaction with temperature rise to 105.6. On September 6 another series of doses to a total amount of 23.5 cc. was followed by a similar reaction with temperature rise to 104. Subsequently smaller doses of bacteriophage were given and the patient received repeated transfusions. She was discharged October 7; evidently too soon, for she was admitted to the Orange Memorial Hospital with osteomyelitis on October 24 and was again treated with intravenous phage. She was discharged March 1, 1934, with persistent sinus and was reported as walking on June 4, 1934.

No. 79, J. R., a boy of 8, was admitted to Bellevue Hospital November 21, 1933, where an appendectomy was performed. Subsequently there was recognized osteomyelitis of the right femur, left tibia, left fibula, left humerus, and left radius as well as suppurative pleurisy. Blood culture of November 27 was positive for *S. aureus*. The record says with 1000 colonies per cc. Bacteriophage treatment was begun on November 29, 1933, and continued until about December 15. The patient remained in the hospital for a year under treatment for the localized areas of osteomyelitis. Many operations were performed for drainage. He was discharged, improved, on December 16, 1934.

No. 37, D. M., a girl of 11, was admitted on November 25, 1932, to the Jamaica (New York) Hospital with cellulitis of the face, which began about November 19. Blood culture taken on admission yielded *S. albus*. Temperature ranged between 102 and 104. Bacteriophage intravenously in divided doses to a total of 36 cc. was administered on November 29 without reaction. After an interval of 9½ hours this treatment was continued to a total amount of 12 cc. in this second series, whereupon there was a chill with cyanosis and rise in temperature to 103.4. On the next day the temperature dropped to 99.6, and did not go above 102 again during her stay in the hospital. There was no further bacteriophage therapy. The patient was discharged December 24, improved.

No. 100, M. D., a girl of 12, was admitted to the Greenpoint Hospital, Brooklyn, on March 26, 1934. On April 13 a simple mastoidectomy was performed. On April 22 the left wrist became painful. On May 12 a thrombosed jugular vein was ligated and opened. The blood culture of May 10 yielded staphylococci and on May 13 a blood culture yielded streptococci. These cultures were not made available for examination by us. Staphylococcus bacteriophage was given intravenously to a total amount of 28.5 cc. on May 13, without evident reaction. The patient recovered and was discharged on May 23, 1934. This case is included in our series with a great deal of reserve. We are inclined to question the validity of the first blood culture. It seems not improbable that this was an ordinary case of streptococcus mastoiditis with jugular thrombosis.

E. H., *No. 30*, a girl aged 15, was admitted to the Long Island College Hospital on August 18, 1932, with sepsis following punctured wound of a toe. The leg was incised on August 19. Blood culture taken August 21 yielded 54 colonies of *S. aureus* per cc. of blood. Stock staphylococcus bacteriophage was given intravenously in divided doses to a total amount of 29.5 cc. on August 24 and also was applied to the wound. Smaller intravenous injections were continued until September 11. Blood cultures on August 25, 29 and September 8 were negative. The patient was discharged on June 28, 1933, with persistent sinuses. On July 26, 1934, she was walking with crutches.

No. 35, H. L., a boy aged 15, was admitted to the Yonkers (New York) General Hospital October 7, 1932, for osteomyelitis of left femur, following an abscess on right elbow which was then healing. Blood culture taken October 11 yielded *S. aureus* and further positive blood cultures were obtained on October 14, 17, 24 and November 4. A staphylococcus vaccine was given subcutaneously on November 5 and 6. On November 11 an extensive operation was performed removing the necrotic cortex of middle third of the femur. Bacteriophage was applied locally at this time. On November 13 Savita* bacteriophage was given intravenously in 2 doses, 0.5 and 1 cc., followed by a chill with cyanosis and temperature rise to 104.8. On November 18 a total amount of 2.5 cc. was given intravenously

* Savita bacteriophage is bacteriophage prepared in a medium containing vegetable proteins supplied by Savita, a meat substitute. This medium was used only for a short period of time in our laboratory.

in 3 doses. On November 19, 6 doses, total amount 15.5 cc., were given intravenously. The patient complained of feeling cold and temperature rose to 104 and fell to 99 to remain down all the next day. Smaller doses were continued up to November 24 and on this day the newly prepared specific bacteriophage was given intravenously, a total of 9 cc. in 2 doses, after which there was a chill at 2 P.M. lasting 45 minutes and temperature rise to 106.6 with fall to 99 at midnight rising again to 101 on third day afterward. Phage was used locally only after this time. He was discharged January 19, 1933, in good condition.

E. B., *No. 99*, a girl of 15, was admitted to the Perth Amboy General Hospital on May 7, 1934, with cellulitis of the face and neck, lobar pneumonia of the upper left lung and embolic lesions in the skin. The admission note states that she was moribund. Blood culture was taken on May 7 and again on May 8 and the doctor has informed us that these cultures were positive for staphylococcus. Laboratory records are not available. Intravenous bacteriophage was started at 8.10 P. M. on May 10 and continued until 1.50 A.M. on May 11, the total amount being 36 cc. intravenously. There was no chill but there was free diaphoresis at 1.45 A.M., and at 4.15 A.M. the temperature had fallen to 101.4. The patient was distinctly better on this day. Smaller injections of bacteriophage were continued for at least 10 days during which time the cellulitis of the face and neck cleared up. Blood cultures were consistently negative after June 5. A metastatic abscess of the left hip was incised and drained on July 7. The lung cleared gradually and she was discharged September 25 in good condition.

No. 110, W. N., a boy aged 16, was admitted to the Alexian Brothers Hospital, Elizabeth, N. J., on July 16, 1934, suffering from sepsis following tooth extraction. Blood culture taken on July 17 gave a growth of *S. aureus* and on July 18 the bacteriophage was given intravenously in divided doses to a total amount of 15.5 cc. Following this there was a slight chill, and diaphoresis. On July 19 a series of 7 intravenous doses to the total amount of 65 cc. was followed by slight chill and sweating. After moderate doses for a few days he was given a total of 85 cc. on July 24 without evident reaction and on July 25 a total amount of 45 cc., after which there was a severe shock and a temperature rise to 107. Small intravenous injections were continued daily during the patient's stay in the hospital. He was sent home from the hospital on August 29 and was able to be up and about during December, 1934. Patient was reported to be doing well on January 15, 1935.

F. D., *No. 74*, a boy aged 16, was admitted to the Mary Immaculate Hospital, Jamaica, N. Y., on November 10, 1933, with a diagnosis of acute osteomyelitis. Blood culture taken November 10 was reported positive on November 13 for hemolytic *S. aureus*. On that account bacteriophage was requested and was furnished by us on November 13, 1933. When this material arrived at the hospital it was decided that the blood culture could not be regarded as positive and therefore the bacteriophage was not used. The boy was discharged from the hospital on November 19. On December 1, 1933 he was readmitted to the hospital and discharged again on December 12, to be readmitted on January 10, 1934, and discharged on January 14. At the time of the third admission there were multiple abscesses in different parts of the body and the doctor informs us that on the basis of the clinical evidence there must have been a blood stream infection. Culture taken from one of these abscesses in January, 1934, yielded *S. aureus*. Autogenous vaccine was given to the patient and his condition was reported as entirely satisfactory on January 14, 1935. This patient is included in our series with considerable reserve but we decided not to exclude him because he appears to have made a recovery from a decidedly questionable bacteremia without the use of bacteriophage. In this series we have included

all patients in whom there is definite reliable evidence of a septicemia with staphylococcus in the blood stream for whom we have been asked to furnish bacteriophage. Whether the bacteriophage was used or not has not been a criterion for including or excluding the patient. As will be seen later this is the only patient in the entire series who recovered without the use of bacteriophage. The others for whom the bacteriophage was not used, succumbed.

No. 32, M. U., a man aged 21, was admitted to the Students Health Service, University of Minnesota, September 23, 1932, following a fracture of the sternum in football practice on September 19. Bacteriophage was requested by telegram on October 5, 1932, and forwarded by air mail. This was given intravenously on October 7 to a total amount of 5 cc. Subsequently a broth bacteriophage was applied to the mediastinal wound. The patient has been reported by McKinley and his associates.[1] He recovered and was able to play football again in November, 1934.

No. 54, H. P., a man, aged 21, was taken ill on April 24, 1933, with sore throat followed by pneumonia. Blood culture taken on May 11 gave a growth of *S. aureus* and there were several subsequent positive blood cultures. Bacteriophage was given first on June 5 and specific autogenous phage was used first on July 10. The patient made a complete recovery. This case has been reported in detail by Dr. W. M. Gilbert.[2]

No. 65, D. M., a man, aged 23, was admitted to the Grasslands Hospital, Valhalla, N. Y., on August 5, 1933, with a carbuncle on right forearm. Subsequently pneumonia and septicemia developed. Blood culture taken on August 31, 1933, yielded 170 colonies of *S. aureus* per cc. of blood. Blood cultures taken on September 1 and September 9 were also positive. Stock staphylococcus bacteriophage was requested and given September 2, 1933, at which time we received a culture from the blood. The bacteriophage was used intravenously from September 2 to September 8. At that time the specific preparation was available and its use begun and continued until October 26. A blood culture taken September 28 remained negative and the patient was discharged as recovered on December 3, 1933. He was admitted again on January 23, 1934, with myocardial insufficiency and ascites. Again he received intravenous bacteriophage from February 14 to February 28 and the ascitic fluid was evacuated. He was discharged February 28. On July 28, 1934, he reported again for treatment of a furuncle. At this time his general condition was good.

No. 68, M. P., female, aged 25, was delivered of her third child at the Greenpoint Hospital, Brooklyn, on August 12, 1934, without laceration. On August 14 she had a chill and temperature rise to 104. Blood cultures taken on August 17, 19 and 28 gave growth of staphylococcus. Those taken on September 15 and September 29 remained sterile. On August 23 a right parametrial pelvic thrombophlebitis was recognized and later a septic nephritis and septic pneumonia. The bacteriophage was given intravenously on September 17, at first in a dose of 0.5 cc., and was gradually increased to 2 cc. morning and afternoon. The patient left the hospital on October 2 and follow-up indicates satisfactory and complete recovery.

No. 28, T. O., male, aged 25, had an abscess of the nasal septum beginning with pain on July 7, 1932; incised on July 14. Patient was admitted to the Long Island College Hospital on July 14. Blood culture taken on July 21 gave positive growth of *S. aureus* and it was positive on several occasions thereafter but only a few colonies appeared at any time. Blood cultures taken on August 8 and 15 remained sterile. Metastatic pneumonia, septic nephritis and pyemic abscesses in various parts of the body were observed and the staphylococcus was found in abundance in all these situations. A bacterial vaccine was injected subcutaneously on August 6, 7 and 8. Bacteriophage was given intravenously on August 9 without any attempt

to produce a shock and daily therafter in doses of 1 cc. until September 13, when the patient was allowed out of bed. He was discharged on September 20 and in December he was entirely recovered and "none the worse from his long and difficult experience."

No. 95, J. B., male, aged 26, had a papule on the right side of nasal septum on April 13, 1934. This extended and was incised on April 17. He was admitted to the West Hudson Hospital, Kearny, N. J., on April 19 and blood culture taken on that day gave a growth of *S. aureus*. Subsequent blood cultures were negative. Bacteriophage was given intravenously on April 22, a dose of 0.5 cc. at 1 A.M.; 1 cc. at 1.40 A. M.; 2 cc. at 2.20 A.M.; 3 cc. at 3 A.M.; 4 cc. at 3.40 A.M.; 5 cc. at 4.20 A.M.; 10 cc. at 5 A.M.; 10 cc. at 5.40 A.M.; 10 cc. at 6.20 A.M.; 10 cc. at 7 A.M. and 10 cc. at 7.40 A.M.; a total of 65.5 cc. in about 7 hours. The patient's temperature remained at 101.6 to 101.8 during this time and was 101.6 at 8 A.M., but rose rapidly to 105 at 10.30 A.M., descending again to 100.6 at 8 P.M. At 9.15 P.M. an intravenous injection of 5 cc. phage was given and at midnight the temperature reached 106, the highest point, descending to 100.6 at 6 A.M., April 23. Beginning at 10 A.M. on April 23, intravenous phage was given every 45 minutes to 7 P.M., a total amount of 75.5 cc. The highest temperature was 102 at 8 P.M. A precisely similar course of treatment was given on April 24 and on this day the highest temperature was 100.4. After that the temperature did not again exceed 99 and the patient was discharged from the hospital on April 29 and on May 7 the face was finally healed without scar.

No. 78, F. D., male, aged 27, developed fever, chills and productive cough about November 4, 1933, and was admitted to Morrisania Hospital on November 9 with physical signs of pulmonary exudate in both lower lobes. The temperature reached 105.4 on November 11 and 106.6 on November 14 and 15. Blood culture taken on November 20 yielded *S. aureus* and fluid from the right pleural cavity on December 19 revealed the same organism. Bacteriophage was given intravenously on November 25 in gradually increasing doses at intervals beginning with 1 cc. at 1.30 P.M. and ending with 7 cc. at 6.40 P.M., the total being 30 cc. This was followed by a chill and temperature rise to 106 at 7.30 P.M. and prompt fall to 99.8 at 8 P.M. Intravenous bacteriophage was continued in smaller doses until December 29, after which time the temperature remained below 99. Blood culture taken on November 30 yielded one colony of staphylococcus and subsequent ones were negative. Thoracotomy was not performed. Roentgenograms revealed a persistent thickened pleura. The patient was discharged as cured on January 6, 1934.

No. 89, E. M., male, aged 28, had osteomyelitis of lower third of right femur for about 20 years. About January 16, 1934, this region became painful and on February 1 he entered St. Peters Hospital, Brooklyn, where an abscess on the lateral aspect of the femur was incised. The pus contained *S. aureus*. The patient developed a septic temperature and blood cultures taken on February 17 and February 19 gave growth of the same organism. On February 22 at 10.25 A.M. 0.5 cc. of bacteriophage was given intravenously and continued in gradually increasing doses at intervals of 30 to 50 minutes until 7 P.M., when a total amount of 75.5 cc. had been given. There was no shock but some increase in sweating at 11 A.M. The temperature rose gradually from 97.8 at 10.25 A.M. to 104 at 8.30 P.M. Morphin sulphate gr. $\frac{1}{4}$ at 2.40 P.M., gr. $\frac{1}{6}$ at 5.30 P.M. and gr. $\frac{1}{8}$ at 7 P.M. may have played a part in suppressing the reaction but this is merely a surmise. On February 25 amputation was done at lower third of right thigh after which the temperature became normal and the amputation wound was healed completely on April 28, when the patient was discharged. The attending surgeon believed that the bacteriophage was without beneficial

effect and the removal of the focus of infection by amputation on February 25 resulted in the change in course of the disease.

No. 71, T. H., male, aged 29, suffered a compound fracture of the right ankle on September 21, 1933. Subsequently he developed septicemia and multiple metastatic abscesses. The blood culture was repeatedly positive with *S. aureus* and *Strep. hemolyticus*, single or mixed together. After a desperate and prolonged illness, during which transfusions, staphylococcus bacteriophage and streptococcus serum were employed, the patient recovered and was discharged from hospital on March 23, 1934. This case has been made the subject of a separate report.[3]

No. 112, E. O., female, aged 31, multipara, was delivered at the Community Hospital, New York City, of a stillborn child on June 26, 1934. Sepsis developed on June 28. Repeated transfusions were given and an abscess in the right broad ligament was drained on July 16. A positive blood culture was obtained on July 23, reported first as hemolytic streptococcus and later recognized as *S. aureus*. The temperature reached 107 on July 21, 23, 24, 27, 29 and August 5, and on July 19 and August 4 it reached 108. The highest temperature observed was 108.6 on July 25, at which time the patient was in a convulsion. Bloody sputum from abscess in the right lung and purulent urine showed abundant staphylococci mixed with an apparently anaërobic bacillus which failed to grow in culture. Blood cultures remained negative except for the one taken on July 23. On July 30, streptococcus serum was given and after further study of the blood culture, staphylococcus bacteriophage was given intravenously in divided doses to a total of 7 cc. This was followed by a chill and temperature rise to 106.4 with drop to 99.2 the next morning. Intravenous bacteriophage was continued in smaller doses daily until August 29 and thereafter in subcutaneous doses until September 28. The patient was discharged November 4 and was reported in perfect health in March, 1935. This case will probably be reported elsewhere in detail by Dr. H. P. MacGregor and his associates.

No. 108, K. H., male, aged 37, injured his left thumb with a piece of steel on May 4, 1934 and was admitted to St. Johns Hospital, Long Island City, on May 18 with osteomyelitis of the thumb from which *S. aureus* was isolated. Blood culture taken on June 20 and another on June 21 gave growth of the same organism. An abscess of the left foot was noted on July 1. Intravenous bacteriophage was given first on July 3, a total of 75.5 cc. in divided doses from 4.50 A.M. to 5.30 P.M. and again on July 6, a total of 75.5 cc. from 11 A.M. to 9.30 P.M. Following this second course the temperature rose to 103 and fell to 99.2 the next morning. On July 10 he received 55.5 cc. followed by a sharp temperature rise to 105 at 6.15 P.M. and a fall to 97 at 4 A.M. following. Another series of injections to a total of 21.5 cc. were given on July 11 and another series on July 13 to a total of 75.5 cc. Apparently the recommended small daily doses of phage were omitted but we are uncertain as to this because the record available to us is not very detailed. Positive blood culture was obtained on September 4 and September 20 and blood culture taken on September 28 remained negative. The patient was discharged in good condition on November 25.

No. 59, A. W., male, aged 39, suddenly became ill on July 10, 1933. He was admitted to the Post-Graduate Hospital on July 12, 1933, and finally discharged on June 2, 1934. His abridged clinical record has been presented in the preceding paper.[4]

No. 56, A. R., female, aged 49, had received treatment for a right ureteral calculus in the Beth El Hospital, Brooklyn, from June 2 to 19, 1933. After ureteral instrumentation the concretion was expelled on June 13. After antiseptic treatment she was discharged on June 19. At home she had an irregular fever, at times as high as 104 and was again admitted to the same

hospital on June 23, with pyelonephritis. Left pleurisy with effusion was recognized on June 25 and pneumonia in both lower lobes was found on June 27. The patient's temperature reached 105 on June 28 after a chill. A blood culture taken June 29 yielded 30 colonies of *S. aureus* per cc. of blood. Intravenous injections of phage were begun at 5.20 P.M. on July 1 and continued at intervals of 40 to 60 minutes until 12.10 midnight, the total amount being 58.5 cc. Twenty minutes later, at 12.30 A.M., July 2, there was a chill lasting 20 minutes and the temperature reached 106.4, falling quickly to 103 at 4 A.M., 101 at 8 A.M. and 99.6 at 4 P.M. on July 2. An intravenous dose of 5 cc. phage was given at noon on July 2 and then doses of 2 cc. were given morning and afternoon, apparently with considerable irregularity, until August 31. Blood culture taken on July 3 yielded 2 colonies of staphylococcus per cc. and one taken on July 8 showed a "few" colonies. Five more blood cultures taken during her stay in the hospital remained negative. Multiple pyemic abscesses appeared and these were treated conservatively. Some resolved without drainage, others healed after aspiration of the pus and some were incised and irrigated with phage. She was discharged on December 29. We are informed that she developed more abscesses after leaving the hospital but was much improved in June, 1934.

No. 88, C. B., male, aged 64, a private patient of Dr. Russell Cecil, developed fever and intestinal stasis about January 1, 1934. A preliminary diagnosis of intestinal neoplasm could not be confirmed by roentgenologic study. About the middle of January a positive blood culture was obtained and a few days later several teeth were extracted. He was seen by us in consultation on January 27, and, after taking a blood culture, which later yielded 218 colonies of *S. aureus*, stock bacteriophage was given intravenously at intervals of about 40 minutes beginning with 1 cc. at 2 P.M. and ending with 26.5 cc. at 6.45 P.M., the total amount being 100 cc. Small intravenous doses were given on the next 2 days. On January 30 at 7.55 A.M. a blood culture was taken which later developed only 12.5 colonies per cc. of blood and then the newly prepared specific phage was given intravenously in 10 cc. doses morning and evening. On February 1 this phage was given in a series of injections to a total of 90 cc. after which there was a chill. Another series of injections, total amount 150 cc., was given on February 8 and this series was followed by a moderate shock reaction. Bacteriophage treatment was then discontinued, contrary to our advice. Blood culture taken on February 11 yielded 42 colonies per cc. of blood. The patient was clinically improved at this time. Subsequently pyuria was recognized with staphylococcus in the urine. Apparently this resulted from a renal infarct. He continued to improve, spent a comfortable summer, after which he returned to his professional work, apparently normal.

Of these 25 patients only 3 were seen by any of us in person. To the others we furnished bacteriophage and suggestions for its use upon request of the attending physicians and our information concerning the clinical features and also the cultures transmitted to us are not primarily our own. Even the 3 patients seen by us (Nos. 57, 86, 110), were seen in consultation after several other physicians had already been consulted by the attending physician.

The Fatalities. The conservative physician ordinarily is reluctant to employ unfamiliar therapeutic measures, particularly if they are believed to be dangerous, until he has exhausted his usual remedies and is compelled to recognize that he is confronted with a desperate or practically hopeless situation. This attitude has been

correct, in our opinion. It is repeatedly and indeed almost uniformly exemplified in the series of 100 cases here presented. We hope, however, that future patients may be given the chance of help offered by intravenous bacteriophage without too great delay after staphylococcus invasion of the blood stream has been recognized. In the present series, several patients died before the bacteriophage was actually used in treatment. In others the course of bacteriophage treatment was interrupted or its use was such as to leave something to be desired. Brief notes on some of these unfortunate cases follow.

No. 26, E. P., a woman, aged 26, was delivered of a macerated fetus on July 16, 1932. Blood cultures taken on July 17 and July 22 yielded *S. aureus*, 80 colonies per cc. of blood on the latter date. On July 26 there was a severe chill and her physician requested bacteriophage which was promptly furnished. However, when the bacteriophage arrived the "patient did not seem very ill and other consultants would not permit phage therapy." On the next day hysterectomy was performed. The patient died on August 4.

No. 31, L. B., a girl, aged 8, developed otitis media on September 14, 1932, followed by extensive inflammation of the accessory nasal sinuses. On September 18, the maxillary antrum was opened and portions of turbinate bodies removed. Cultures from the sinuses yielded *S. aureus* but there appears to be no record of a positive blood culture. Bacteriophage was requested on September 23 and was promptly supplied. Intravenous injections of the phage were given: 5 cc. on September 24, 2 cc. on September 25, 4 cc. on the 26th, 5 cc. on the 27th and on the 28th, 15 cc. on the 30th, 10 cc. each on October 1, 2, 3, 4 and 5. Metaphen and Pregl's iodin were also given intravenously and several transfusions were given. The necropsy on October 5 disclosed purulent pachymeningitis, general phlebitis of the dural sinuses with obliteration of the cavernous sinuses, purulent adhesive pericarditis, metastatic abscesses of the heart muscle and of the kidneys.

No. 36, P. S., a boy, aged 16, received a blow on the chest wall about November 2, 1932. On November 15, he was admitted to hospital, irrational, with diagnosis of acute rheumatic fever. On November 16, the spinal fluid contained 10 cells per c.mm., with a trace of globulin; thick pus was aspirated from the chest wall and a blood culture was taken, which yielded *S. aureus* by the next day. Thereupon bacteriophage was requested and intravenous injections started: 0.5 cc. at 11.40 A.M., 1 cc. at 12.10 P.M. Then the thoracic wall was incised and a fractured rib disclosed. Following the operation a dose of 4 cc. of phage was given intravenously at 2 P.M., at which time the patient was evidently failing. At 2.30 P.M. there was no response to stimulation and at 3.46 the patient died. The autopsy presented the picture of general sepsis.

No. 42, M. H., a girl, aged 17, with osteomyelitis of the pelvic bones, invading the hip joint, was relieved of her blood-stream infection following bacteriophage therapy but developed severe secondary infection of the operative wound with hemolytic streptococci and other bacteria and eventually died. Her record has been presented in an earlier paper.[5]

No. 44, V. M., female, aged 21, ill since December 31, 1932, developed local pain and swelling in the left parotid region about January 14, 1933. Upon admission to hospital, January 21, a blood culture was taken which yielded staphylococci. The parotid region was incised and pus found on January 23. Bacteriophage was requested on January 24 and promptly supplied by messenger but the patient died at 1.30 P.M. on this date before the bacteriophage could be used.

No. 45, E. C., a girl, aged 11, had a blood culture taken January 24, 1933, which yielded countless colonies of *S. aureus*. Bacteriophage was requested January 26 and immediately supplied. Some of it was used, but not more than 20 cc., because the remainder was returned to us. Death occurred on January 26 and autopsy disclosed empyema, multiple abscesses in myocardium and osteomyelitis of the right clavicle.

No. 48, C. O., a girl, aged 16, was admitted to hospital with acute left mastoiditis on January 25, 1933, and treated by mastoidectomy on January 28. Bacteriologic findings on material from this operation are not available. Blood culture on February 3 yielded *S. albus*. On February 4 and February 6 blood culture gave negative result. On February 7 the lateral sinus was exposed and the left jugular vein ligated. On February 18 blood culture again gave growth of *S. albus*. Bacteriophage was requested and supplied by us on February 18. A second blood culture, which appears to have remained negative, was taken about 6 P.M. on this day and then the bacteriophage was given intravenously at 6.20 P.M., a dose of 1 cc. and subsequently at intervals of 1 hour doses of 2–6–8–5 cc. up to 10.20 P.M., the total amount being 22 cc. There was no evident reaction. On the next day, February 19, an intravenous dose of 5 cc. was given at 1 P.M. and another of 8 cc. at 2 P.M. There was a chill at 2.25 P.M. On February 20 an intravenous injection of 2 cc. was given at noon and on February 21 at 11.30 A.M., 2 cc., and again at 8 P.M., 2 cc. On February 22 a blood culture was taken, which appears to have remained negative, and then the patient received a series of intravenous injections from 11.25 A.M. to 9.30 P.M., the total amount being 153.5 cc. At 8 P.M. there was some mental confusion but there was no recognized chill. An injection of 5 cc. was given on February 24 and again on February 26 and February 28, but apparently no more phage after that. Transfusions were given: 400 cc. on March 7 and 500 cc. on March 11. On March 11 the jugular bulb was explored. The patient died at 3.55 P.M. March 13. Without wishing to be too critical, one may nevertheless express some skepticism about the validity of the two positive blood cultures in which *S. albus* was recognized. It must also be evident that the clinical application of the bacteriophage lacked precision. This record is presented as an example of lack of sympathetic understanding of bacteriophage therapy and a lack of intelligent clinical application of this agent. We include it among our failures, although we suspect that the patient actually died of a streptococcus mastoiditis complicated by sinus thrombosis. The record of temperature and pulse has not been made available to us.

No. 51, A. R., male, aged 27, had chronic recurrent osteomyelitis with amputation of leg in 1918. He was admitted to hospital on March 3, 1933, and an operation was performed on the femur on April 28. On April 29 at 4 A.M. the temperature reached 106.4 and a blood culture taken at this time yielded *S. albus*. His condition steadily grew worse. Bacteriophage was requested and supplied on May 3 and beginning at 10.45 A.M. on this date a series of 13 intravenous injections was given, the total amount of phage being 75.5 cc. There was no evident reaction. The patient died at 6 A.M., May 4.

No. 55, S. K., female, aged 31, had a furuncle on her chin on June 12, 1933. She was admitted to hospital at 1.45 P.M. on June 16 at which time her temperature was 101.8, rising steadily to 105 at midnight. Blood culture taken on June 16 yielded a growth of staphylococcus on the next day. Bacteriophage was then requested and supplied and at 11.20 A.M. June 17, an intravenous injection of 4 cc. was given. There was no reaction. The patient died at 11.45 A.M.

No. 57, A. N., male, aged 57, developed an abscess near his left knee on June 12, 1933. He was admitted to hospital. A blood culture positive for

S. aureus was obtained on July 8, 1933 and bacteriophage was supplied by us on July 10. On August 4, he was transferred to a second hospital, where the bacteriophage treatment was resumed on August 17 with the specific preparation. The blood culture became negative and on August 24 we were informed that the patient was much improved. Bacteriophage therapy was discontinued on August 31; a note in the record submitted to us a year later says "no more bacteriophage obtainable." The patient died October 8, 1933.

No. 64, H. C., male, aged 41, was admitted to hospital August 28, 1933. Blood culture taken on this day gave positive growth of staphylococcus on August 30. Spinal fluid taken on August 28 was under increased pressure with slight increase of cells, and another spinal fluid taken on August 29 gave a positive growth of staphylococcus. Bacteriophage was requested and supplied on August 31. At this time the neck was rigid and the patient comatose. Intravenous injections were started at 11.50 A.M. and continued until 3.30 P.M., the total amount of phage being 15.5 cc. Death occurred at 4.10 P.M. and autopsy disclosed an acute vegetative endocarditis and embolic abscess of the brain.

No. 69, A. M., male, aged 37, had a small furuncle inside the nostril on the nasal septum on September 14, 1933. The swelling had extended to the forehead and eyelids when he was admitted to hospital on September 19. Record of blood culture has not been given to us but we were informed that the patient had staphylococcus septicemia on September 23, 1933, when the bacteriophage was first requested and immediately supplied by messenger. The patient died before the bacteriophage reached the hospital. The final diagnosis was cavernous sinus thrombosis and meningitis.

No. 73, R. S., female, aged 31, had been under treatment for mastoiditis 4 months. At some time before her last illness she got a splinter in her finger and a felon had developed but this was not treated by a physician. On November 1, 1933 she had a violent headache and was admitted to hospital on November 2. Blood culture taken then was sent to us on November 3 with positive growth of *S. aureus*. Bacteriophage was supplied at once but the patient died on November 3, before any of it was used.

No. 85, E. O., female, aged 24, had a small furuncle on her face on December 24, 1933, which was opened. On December 31 she had a chill and on January 1 her temperature reached 105. She was admitted to hospital on January 6 and a blood culture taken on this day yielded *S. aureus*. The culture was submitted to us on January 9 with request for bacteriophage which was at once supplied. On January 10, intravenous injections of the phage were begun at 4.15 P.M. and continued until 12.25 A.M., the total amount given being 75.5 cc. There was no reaction and the phage therapy was discontinued. The patient died on January 18, 1934 at 1.25 A.M.

No. 87, V. H., a girl, aged 12, had an infected blister on her heel on January 7, 1934. On January 14, she was admitted to hospital with a suppurating left knee joint and osteomyelitis of left femur and left shoulder. Blood culture taken either January 14 or 15 yielded 29 colonies of *S. aureus* per cc. of blood. Bacteriophage was requested on January 25. The intravenous injections were started on this day and continued to January 28, the total amount administered in these 4 days being 90 cc. The attending physician then discontinued the use of bacteriophage. The blood culture taken on January 27 showed 4 bacteria per cc. of blood and that taken on January 31 as well as subsequent blood cultures was negative. Many transfusions were given after January. The patient died on June 20, 1934, nearly 5 months after bacteriophage therapy was discontinued.

No. 93, W. J., male, aged 46, was admitted to hospital on February 26, 1934 and his left kidney was removed on March 1. On March 2 his tem-

perature rose to 102 and on March 19 it reached 105, remaining above 104 thereafter until death. A blood culture, apparently taken on March 19, yielded growth of staphylococcus. Bacteriophage was requested on March 20 and supplied at once. However, none was ever given to the patient. On March 22 an exploratory thoracotomy was done with negative findings. The patient died on March 23.

No. 102, L. S., male, aged 34, suffered a wound of thumb by broken glass on December 24, 1933. A severed tendon was sutured on the same day. Blood culture taken on January 15 was negative but that of January 19 yielded *S. aureus*. Subsequently many positive and some negative blood cultures were obtained. There were 23 operations for drainage of suppurating foci and 30 transfusions. After about 5 months, bacteriophage was requested on June 6, 1934, as a last resort. On this day the patient received 75.5 cc. intravenously in a series of injections. Smaller doses were continued daily until June 13. A blood culture taken June 9 was positive for staphylococcus. Death occurred at 2.30 A.M. on June 15.

No. 106, H. M., male, aged 19, was admitted to hospital on April 30, 1934, with infected hand and diabetes. Blood culture taken on May 7 gave growth of *S. aureus*. The hand was incised on May 9, the arm on May 10, the elbow on May 11 and the arm on May 13. Further operations included chest aspiration and incision of leg on May 19, incision of heel on May 22, incision of forearm on May 26, aspiration of abscess in neck on June 2, incision of buttock on June 4 and incision of arm on June 9. A stock bacteriophage was employed from time to time as follows: May 17, intravenously, 5 cc.; May 26, applied to wounds; May 30, a course of intravenous injections; June 2, local application of 10 cc. to abscess in neck; June 7, a course of intravenous injections with shock and temperature rise to 106. Our service was requested on June 23 and on the next day our stock bacteriophage was given in a series of intravenous injections to a total amount of 41.5 cc. Small injections were given on June 27 and July 2. Specific bacteriophage was prepared as rapidly as possible but with unusual difficulty and delay. It was finally ready but did not reach the bedside of the patient (Philadelphia) in time to be used. The patient died July 3, 1934.

No. 113, R. M., male, aged 15, had pain in his abdomen, right hip and right thigh upon awakening August 2, 1934. He was admitted to hospital on August 3. Blood culture, taken apparently on August 4, gave positive growth of *S. aureus*. On August 6 an intravenous injection of 20 cc. of 1% mercurochrome was given. Later on this same day bacteriophage was requested and the stock asparagin preparation was given intravenously in divided doses to a total amount of 29.5 cc. followed by chill and temperature rise to 106.8. On the next morning the temperature was 99. Contrary to our advice, another series of intravenous doses was administered to a total of 19.5 cc. with chill and temperature rise to 105.2. On August 8 a third series to a total of 59.5 cc. was given without reaction. The patient appeared better and the temperature was lower. Blood cultures, however, remained positive. Bacteriophage therapy was then discontinued. A series of irradiated transfusions was given from August 9 to August 16. On August 17 bacteriophage injections were started again and given daily in large amounts: 70.5 cc. on August 17, 19.5 cc. on August 18, 60.5 cc. on August 19, 80 cc. on August 20, 20 cc. on August 21 and 20 cc. on August 22. The patient died at 11.45 P.M., August 23.

It is, perhaps, essential to emphasize the fact that these patients were not under our control. We have supplied bacteriophage upon request to any qualified physician who furnished reasonably reliable evidence that his patient had a staphylococcus bacteremia. Along

with this we have included advice in regard to use of this agent, which may or may not have been followed. We have earnestly requested that the positive blood culture, preferably one of the original plates, be delivered to us at the earliest possible moment and that we be furnished with a record of the case upon its completion. We are very grateful indeed for the records which have been provided by the different physicians and hospital executives. Without these this discussion would not be possible. For scientific purposes, it is perhaps fortunate that there has been such a lack of uniform practice in using the bacteriophage. One thus has presented a variety of contrasts in therapy and also some contrasts in results. Such records of past experience guide a future course through similar problems.

The few selected fatalities briefly reviewed above illustrate some of the most marked departures from the method of treatment which we recommend. In some instances a more fortunate therapeutic program might have led to a better outcome. We hesitate to pass judgment however. Certain it is that many patients in the series succumbed to the disease even though the treatment represents the best of which we possess knowledge. One has to recognize that staphylococcus bacteremia is a disease of high mortality and that in many instances it has already passed beyond human control before the diagnosis is made.

Comment. The appraisal of a therapeutic agent on the basis of clinical experience is beset with difficulty. The human material is lacking in uniformity. One takes the patients as they come. It has been suggested that alternate patients might be observed as controls, intentionally omitting the use of bacteriophage. Such a program would require a control of the clinical material which we have lacked. Furthermore, we should be loath to attempt such a control series even if the clinical material were available under our control. One occasionally hears that in staphylococcus bacteremia the death rate without bacteriophage is only about 50%, but one does not find the recorded observations on which such a loose statement may be based. Apparently those who have observed such recoveries have been satisfied to make their diagnoses on clinical evidence only or upon a single positive report of growth of staphylococcus of undetermined variety in a flask of broth, or in some instances without any distinct attempt to identify the sort of microbe present in the blood culture. Previous to the use of bacteriophage our observations of staphylococcus infection of the blood stream, proven by reliable blood cultures, had made us believe that recovery was extremely rare.

Though each individual in this series has presented peculiar features, nevertheless there are several which may be placed in a control group, not by our intent, but by circumstances wholly beyond our influence. For Patient 26, for example, the bacterio-

phage was supplied but not used, apparently because she was not regarded as sick enough to warrant it. Patients 44, 69, 73, 93 died before any bacteriophage was used. Patient 51 died within 20 hours after beginning use of the phage, which produced no recognizable reaction. Patient 64 was comatose when the bacteriophage was started and died 4 hours later without reaction. In 2 instances (Patients 26 and 93), the clinical condition upon arrival of the bacteriophage was good enough to allow further operative incision. In the other 5, the disease had already reached a clinically hopeless stage. These 7 may properly be regarded as controls.

In the discussion of the fatalities there are mentioned 12 other patients whose records indicate inadequate use of bacteriophage or complicating factors in the disease or in the therapeutic measures employed. In some of these the bacteriophage was discontinued after clinical improvement and the disease again progressed to death, as for example Nos. 57, 87 and 114.

In the group of 25 survivals, Patient 100 appears not to have been helped by the bacteriophage and in fact there is good reason to doubt the existence of staphylococcus bacteremia in this case. Patient 74 did not receive any bacteriophage and the evidence of a blood stream infection in this case seems to be quite inadequate. The remaining 23 patients who recovered seem to have received benefit from the bacteriophage and in several of these the effect may properly be said to have been life-saving.

Summary. 1. Staphylococcus septicemia occurs in both sexes and at all ages but during adult life is somewhat more common in males.

2. Brief notes are presented on 100 cases, No. 16 to No. 115 in our series of staphylococcus bacteremias receiving our bacteriophage service. Of these patients 75 died and 25 survived. This is a much better percentage than is found in published reports of this condition.

3. Staphylococcus infection of the blood stream is definitely influenced by the intravenous administration of potent bacteriophage and when wisely employed the bacteriophage is helpful, sometimes even life-saving in the treatment of these patients.

REFERENCES.

1. McKinley, C. A., Kinsella, T. J., and Radl, R. B.: Acute Essential Hypertension Precipitated by Mediastinal Abscess, Arch. Int. Med., **54**, 645, 1934.

2. Gilbert, W. M.: Staphylococcus Bacteremia. Report of a Case with Recovery, Colorado Med., **31**, 66, 1934.

3. Moore, D. C., Blinn, A. B., and MacNeal, W. J.: Compound Fracture Complicated by Prolonged Streptococcus and Staphylococcus Septicemia, With Recovery, Am. J. Surg., **29**, 143, 1935.

4. MacNeal, W. J., and Frisbee, F. C.: Bacteriophage Service to Patients with Staphylococcus Septicemia, Am. J. Med. Sci., **191**, 176, 1936.

5. MacNeal, W. J.: Specific Treatment of Septic Infections, Particularly with Aid of Bacteriophages, Ibid., **187**, 628, 1934.

CLINICAL AND ELECTROCARDIOGRAPHIC PICTURE OF CORONARY OCCLUSION PRODUCED BY RUPTURED ANEURYSM OF THE ABDOMINAL AORTA.

By Albert H. Elliot, M.D.,
RESEARCH ASSOCIATE, DEPARTMENT OF CARDIOVASCULAR RESEARCH, COTTAGE HOSPITAL,
AND
Richard D. Evans, M.D.,
ATTENDING PHYSICIAN, DEPARTMENT OF INTERNAL MEDICINE, COTTAGE HOSPITAL, SANTA BARBARA, CALIF.

Much has been written on the differential diagnosis of coronary occlusion, especially in regard to the accuracy with which this condition may mimic acute abdominal disturbances. Lately, attention has been called to the antithetical problem of misinterpreting acute abdominal symptomatology as coronary disease.[1] The electrocardiogram is an invaluable aid in this differentiation if used with a knowledge of its limitations. Occasionally it is unchanged in coronary occlusion. The following report demonstrates the opposite situation, namely, that electrocardiographic changes typical of coronary occlusion may occur in the absence of that accident.

Case Report. A white man, aged 59, was first seen on January 17, 1934, complaining of headache and fatigue. He had had scarlet fever in childhood and a cholecystectomy for gall stones 9 years before. There were dyspnea on slight exertion and a history of 3 attacks of auricular fibrillation in the last 3 years. On physical examination, the pulse rate was 112, and the blood pressure was 165 systolic and 120 diastolic. There was a soft systolic blow localized over the precordium. In addition, there were moderate exophthalmos and lid lag. The left pupil was slightly larger than the right, though both were round and reacted to light. The knee jerks were active. Orthodiagraphic measurements were: transverse cardiac diameter, 13.9 cm.; transverse diameter of the chest, 26 cm. The thoracic portion of the aorta was slightly ectatic. The Kahn test of the blood was negative. The basal metabolic rate was +1%; other laboratory procedures were uninformative.

On April 27, 1934, he was brought to the Cottage Hospital in an ambulance from a bath house on the beach, where he had been picked up unconscious. He was in coma and extremely dyspneic. The systolic arterial pressure was 50; the diastolic, 40. The radial pulse was weak and at times unobtainable. The apex heart rate was 120 and the sounds were distant but regular. Râles were heard at the bases of the lungs posteriorly. The remainder of the examination, including the abdomen and reflexes, was not remarkable. A catheterized urine specimen was free of sugar and acetone bodies.

An electrocardiogram was strikingly changed as compared with a previous one (Fig. 1) taken, January 17, 1934, in which the only abnormality was pronounced left-axis deviation. On the new tracing obtained 2½ hours after hospital entry (Fig. 2), there was a rate of 90, disappearance of the left-axis deviation, an extremely high take-off of the *T* waves in Leads 2 and 3, and a normal Lead 4 as obtained by chest electrodes. This is a "*T*3" type of tracing,[2] showing the changes frequently encountered in recent coronary occlusion and suggesting that the infarcted area is near the base of the heart.

Death occurred a few hours after hospital entry. The clinical diagnosis was acute coronary occlusion.

Necropsy (11 hours after death): The abdominal part of the aorta was dilated to a circumference of 13 cm. from a point 12 cm. proximal to the bifurcation and extending distally into the origins of the common iliac arteries. There was a transverse rupture, 5 cm. in length, of the posterior part of the wall, 10 cm. proximal to the bifurcation, with extensive retroperitoneal hemorrhage. The aortic wall was thickened throughout this region, the intima being friable, and mottled with yellow and white plaques, but containing little lime. The heart weighed 500 gm. and was unchanged

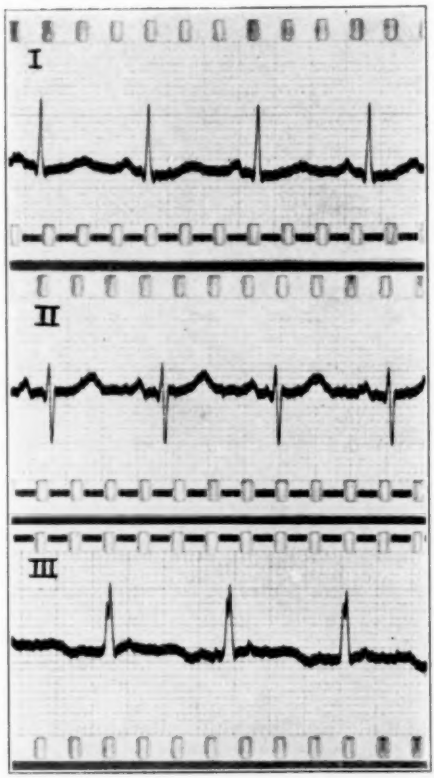

FIG. 1.—Electrocardiogram taken 3 months before death.

except for pronounced thickening of the walls of the coronary arteries. This was particularly true of the descending branch of the left and of the main stem of the right. The lumens were patent throughout, though in places considerably narrowed. The myocardium everywhere was red-brown, and especially careful search failed to reveal any scars or areas of softening. In sections of the aorta, moderate thickening of the intima with fibrous tissue was seen, as well as the characteristic syphilitic changes of perivascular round-cell infiltration of the adventitia and media. In sections from several portions of the myocardium, the muscle fibers were widened and stained well. There was no fibrosis.

Comment. To our knowledge, the diagnosis of ruptured aneurysm of the abdominal part of the aorta has not previously been confused with coronary occlusion. Usually, the prominent symptom of low

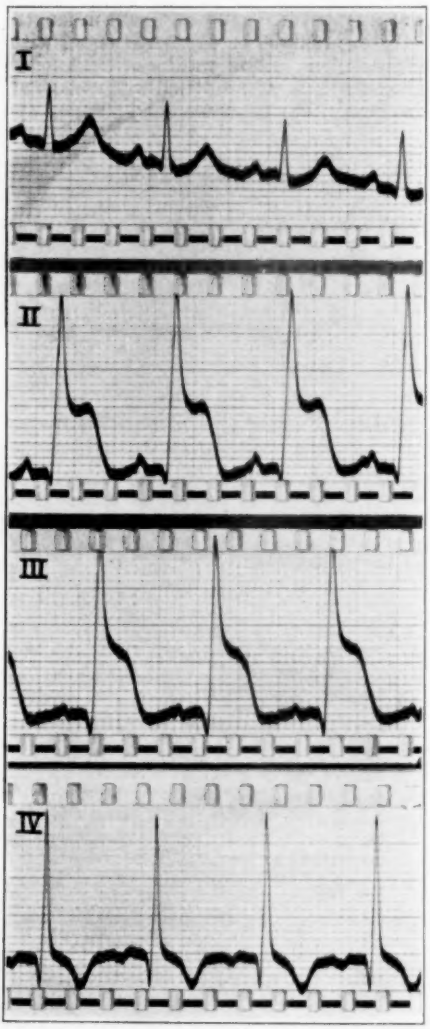

FIG. 2.—Electrocardiogram taken after attack of unconsciousness, a few hours before death.

back pain serves to focus the attention away from the heart and, while the diagnosis may not at first be evident, acute cardiac disease need not be considered.

White *et al.*[3] have recently reported a case of dissecting aneurysm of the thoracic part of the aorta wrongly diagnosed as coronary occlusion. In retrospect, they explain that the correct diagnosis should have been suggested by the lack of sufficient electrocardiographic abnormality. This is particularly interesting to us, as in this case we were confronted with typical electrocardiographic evidence, apparently confirming the erroneous diagnosis of coronary occlusion.

Acute changes in the *R–T* and *S–T* segments of the electrocardiogram are associated (*a*) with a sudden disturbance of the metabolism of the heart mediated through changes of certain of the constituents of the blood, and (*b*) with sudden partial or total deprivation of the blood supply to a portion of the myocardium. To the first group belongs the changes associated with various toxemias, such as pneumonia[4] and uremia,[5] in which the *T* waves have been noted to be of the coronary type. Likewise here are classified the electrocardiographic alterations encountered in diabetic coma (Faulkner and Hamilton)[6] and insulin shock, or in the abrupt but less serious fluctuations of blood-sugar level, dependent upon improper treatment. In diabetes, according to Soskin *et al.*,[7] the storage and/or utilization of glycogen is interfered with. Following excessive doses of insulin, the energy production of the heart muscle is handicapped because of the too rapid lowering of the blood sugar and depletion of the supply. Hence, the final effect of too little or too much insulin is similar. Decreased amplitude and increased slurring of the *Q–R–S* complexes and a tendency of the *S–T* segment and *T* wave to shift in a direction opposite to the major initial complex were noted. Siegel[8] has likewise shown that, if the production of lactic acid from its precursors, sugar and glycogen is interfered with (as in diabetes), the *T* waves become flattened.

Finally, to this first group may be added the observations of Katz *et al.*,[9] who found that general anoxemia in normal persons produced diminution in the amplitude of the *T* waves, at times leading to inversion, without the occurrence of pain. At the same time the *S–T* segment became depressed. Similar changes were found in patients with angina pectoris, of whom 2 out of 6 had mild pain.

As regards the second group, the electrocardiographic changes of coronary occlusion are well known. The ischemia may be relative as a discrepancy between the demands of the heart and its blood supply (Lewis[10]), or absolute when a portion of the myocardium is totally deprived of its circulation. The lumens of thickened coronary arteries may be adequate to provide sufficient nourishment for a heart beating at a normal rate, but inadequate for the same heart speeded up by exercise, thyrotoxicosis, fever, etc.

In the present instance, the explanation appears to be that, though the coronary arteries had considerably thickened walls, they supplied enough blood to the heart muscle to prevent anginal symptoms and electrocardiographic changes. Following the hemorrhage, however, with attendant reduction of the circulating blood volume and shock, the myocardium was no longer adequately nourished, as demonstrated by the second electrocardiogram. The thickened coronary arteries probably contributed to this effect, and, had the patient lived longer, gross changes of softening might have been recognized in the heart.

Summary. An instance is reported of ruptured aneurysm of the abdominal part of the aorta in which, because of coma, the subjective symptomatology could not be obtained. The clinical picture strongly suggested shock following coronary occlusion. Electrocardiographic changes, which were characteristic of and before death were diagnosed as those of coronary occlusion, are seen in retrospect to have been probably due to a relative ischemia of the myocardium without infarction. This ischemia depended on thickened coronary arteries and the reduced circulating blood volume following hemorrhage.

We wish to thank Dr. Franklin R. Nuzum for permission to report this case.

REFERENCES.

1. Barker, P. S., and Wilson, F. M.: Abdominal Disease Simulating Coronary Occlusion, Am. J. Med. Sci., **188**, 219, 1934.

2. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), Heart, **14**, 195, 1928.

3. White, P. D., Badger, T. L., and Castleman, B.: Dissecting Aortic Aneurysm Wrongly Diagnosed Coronary Thrombosis, J. Am. Med. Assn., **103**, 1135, 1934.

4. Abt, A. F., and Vinnecour, M. J.: Electrocardiographic Studies During Pneumonia in Infants and Children, Am. J. Dis. Child., **47**, 737, 1934.

5. Wood, J. E., Jr., and White, P. D.: Electrocardiogram in Uremia and Severe Chronic Nephritis With Nitrogen Retention, Am. J. Med. Sci., **169**, 76, 1925.

6. Faulkner, J. M., and Hamilton, B. E.: Electrocardiogram in Diabetic Coma, Am. Heart J., **8**, 691, 1933.

7. Soskin, S., Katz, L. N., Strause, S., and Rubenfeld, S. H.: Treatment of Elderly Diabetic Patients With Cardiovascular Disease: Available Carbohydrate and the Blood Sugar Level, Arch. Int. Med., **51**, 122, 1933.

8. Siegel, quoted by Smith, K. S.: Nutrition of the Heart in Relation to the Electrocardiogram and Anginal Pain, Lancet, **1**, 632, 1933.

9. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects: Its Bearing on the Mechanism of Attacks of Angina Pectoris, Am. Heart J., **9**, 771, 1934.

10. Lewis, T.: Angina Pectoris Associated With High Blood Pressure and Its Relief by Amyl Nitrite: With a Note on Nothnagel's Syndrome, Heart, **15**, 305, 1929–1931.

PERSISTENT PAIN IN THE SHOULDER REGION FOLLOWING MYOCARDIAL INFARCTION.

By Joseph Edeiken, M.D.,
INSTRUCTOR OF MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
AND
Charles C. Wolferth, M.D.,
PROFESSOR OF CLINICAL MEDICINE, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.)

The material presented in this report consists of 14 cases in which more or less constant and persistent pain in the shoulder region developed within a period of 4 months after acute myocardial infarction. In 3 cases the shoulder pain developed almost coincidentally with the acute attack and in 4 other cases within a period of 4 weeks. In the other 7 cases the pain developed 1 to 4 months after the acute attack. The diagnosis of myocardial infarction in all cases was confirmed by electrocardiograms including both limb and chest leads. In 11 of the 14, tracings were made during both the early and late stages of infarction; in 3 during the late stage only.

Case Reports. Case 1.—P. M., a white male, aged 52, developed acute infarction of the anterior or apical portion of the left ventricle on May 29, 1933. The acute pain centered in the upper part of the chest and first radiated down the left arm and later down both arms. He remained in the hospital for 25 days, during which time he developed continuous pain in the left shoulder region, which radiated down the left arm. Movement of the shoulder, although not restricted, caused temporary increase of the pain.

Six months after the initial attack he suffered another attack with pain similar to the first. Thereafter the pains in the left shoulder and arm increased. Since that time he has been subject to anginal attacks, and although the distribution of pain is similar to that of the continuous pain, he states that the anginal pain is different. He could not describe the difference, except that the one pain was continuous and the other paroxysmal. The anginal pains, however, were promptly relieved by the inhalation of amyl nitrite. During the 3 months following the second acute attack, the continuous shoulder pain became worse and a so-called "trigger zone" developed over the upper part of the left scapula, pressure over which caused knifelike pain in the left shoulder, left breast and down the left arm.

Neurologic examination by Dr. William G. Spiller failed to reveal any evidence of spinal cord disease. Spinal fluid examination was normal. Roentgen ray of the left shoulder was negative; of the spine showed slight lipping of the bodies of the vertebræ. Irradiation therapy of the upper spine and left shoulder region was instituted but not completed, since he insisted on discharge from the hospital. On his way home he suffered a circulatory collapse, but recovered from this attack. Later he reported that he was somewhat improved, attributing the improvement to the irradiation. However, he still suffered considerable pain.

CASE 2.—S. S., a white male, aged 62, on May 16, 1929, was suddenly stricken with severe pain across the front of the chest, radiating to the left arm, the neck and the back. A diagnosis of coronary occlusion was made and he was kept in bed 16 weeks. When first seen by one of us (J. E.) in October, 1929, he complained of attacks of severe substernal pain, radiating down the left arm, up to the neck and to the back, provoked by exertion, excitement or talking too much. An electrocardiogram made at that time showed inversion of *T*–2 and *T*–3 and a deep *Q* II and *Q* III. About this time he first noted continuous pain in the left shoulder and discovered that pressure over the upper portion of the left scapula produced a pain which radiated to the left shoulder, down the left arm and up the left side of the neck. The pain produced by pressure over the scapula was similar to the pain of the attacks provoked by exertion or excitement, except that it was less intense and did not radiate to the anterior portion of the chest.

He was again seen in October, 1934. The shoulder pain had continued throughout the entire 5-year period, being of about the same grade of severity despite many different types of treatment. Movement of the shoulder was not impaired. The trigger zone persisted throughout the entire period. The anginal attacks, however, were more easily provoked by exertion or excitement than 5 years previously. Roentgen ray of his spine (cervical and dorsal) and left shoulder failed to reveal any abnormalities.

CASE 3.—D. S., a white male, aged 55, had attended the Medical Outpatient Section of this hospital since April 6, 1931. The diagnosis made was emphysema and chronic bronchitis. Following an absence of several months, he returned to the section on January 12, 1933, complaining of pain of 3 months' duration in the shoulder joints, much more marked on the left. The pain was severe, constant, burning in character, and extended down to the left elbow and also over the left pectoral region. Examination of the left shoulder revealed nothing except some restriction of motion. The pain dated from a cardiac attack in which he was, in his own words, "saved from expiring by the attention of a private physician who gave him needles in his left arm." He also complained of occasional attacks of paroxysmal dyspnea, accompanied by severe substernal pain radiating to the left shoulder. Following these attacks the pain in the shoulder was increased in intensity. His electrocardiogram was of the type found in the healed stage of infarction of the posterior wall of the left ventricle. The shoulder pain had decreased somewhat by May, 1933. He was seen again, November 3, 1934, when the pain had entirely disappeared.

CASE 4.—M. L., a white male, aged 58, was in fair health until July 12, 1933. Beginning at that time, he had a succession of three attacks thought to be due to coronary occlusion. The pain centered over the precordial area and radiated down the left arm. He was kept at rest for 3 months and returned to work on October 15, 1933. On November 11, he had an attack of coronary occlusion which caused grave circulatory collapse. As in the earlier attacks the pain was greatest in the precordial area and radiated down the left arm. An electrocardiogram revealed the presence of recent infarction involving the anterior wall of the left ventricle. He was kept in bed for 6 weeks. He gradually regained his strength and had no complaints until the early part of February, 1934. At that time he began to complain of pain, greatest in the region of the left biceps muscle, but also involving the left shoulder. The pain was constant, of an aching character and radiated down the left arm. It was worse at night, requiring sedatives. Examination showed restriction in motion of the arm posteriorly but no tenderness over the joint or muscle. Roentgen ray examination of the left shoulder, humerus and cervical and upper dorsal spine, failed to

disclose any abnormality sufficient to account for his pain. Many abscessed teeth were found which were later removed. Smears of prostatic secretion contained about 25 leukocytes per high-power field and prostatic massage was instituted. These measures as well as diathermy and baking were apparently without effect. He received deep Roentgen ray therapy to the cervical and upper dorsal regions on November 10, 1934. Improvement was noted after several days and complete relief occurred in 3 weeks.

Case 5.—W. F. A., a white male, aged 48, was admitted to this hospital (service of Dr. Stengel) on February 13, 1934, 2 days after the onset of a severe attack of coronary occlusion, with severe pain in the substernal area radiating to the precordium. An electrocardiogram revealed the presence of acute infarction involving the posterior wall of the left ventricle. Although at the time of admission, he was critically ill, he improved fairly rapidly and insisted on leaving the hospital on February 21, 1934. He was next seen on October 8, 1934, by our colleague, Dr. F. C. Wood. At that time he felt fairly well at rest; however, exertion or excitement produced a heavy tearing discomfort in upper sternal region. He tired easily but had no dyspnea. He had suffered a constant pain, "like a wrench," in the left shoulder, which had begun while he was confined to bed during the acute attack 8 months before. The pain had recently shifted from the left to the right shoulder.

Case 6.—W. J. R., a white male, aged 44, was seen in consultation September 17, 1934. On July 31, 1934, he had an attack which was diagnosed acute coronary occlusion. The diagnosis was confirmed by electrocardiogram. His acute pain began in the left shoulder and arm and later involved the substernal region. Since the attack he has had pain in the left shoulder and arm, not relieved by nitroglycerin. The pain is almost constant, but does not prevent him from sleeping and is not affected by moving the arm or walking about. There were no points of tenderness along the nerve trunks, nor in the muscles of the shoulder. There was no restriction nor pain on movement of the shoulder. Muscular strength of the shoulder muscles was preserved.

Case 7.—S. S., a white male, aged 58, was admitted to this hospital (service of Dr. Stengel) July 23, 1932. He had suffered from angina pectoris for a number of years, but on July 21, 1932, had an attack of coronary occlusion with an overpowering feeling of compression of his chest. The electrocardiogram showed infarction of the anterior wall of the left ventricle. Convalescence was uneventful until the first week in August when he developed pain in the left shoulder. The pain increased when he was allowed out of bed and continued as a constant ache in the left shoulder.

A focus of infection was sought. Several abscessed teeth were discovered and removed, apparently without influencing the shoulder pain. Roentgen ray of the shoulder, May 31, 1933, disclosed the following: "There is no evidence of calcified subacromial bursitis on the left, but there is a little calcareous deposit in the right so-called subacromial bursa, best visible with the arm in internal rotation." Roentgen ray of the spine on June 5, 1933, disclosed minimal hypertrophic osteo-arthritic changes about the bodies and articulating processes of the lower cervical and upper dorsal vertebræ. He was given Roentgen ray treatment to the cervical spine but without relief. Roentgen ray treatment directly over the left shoulder was advised but the patient did not return for it. He was again seen in July, 1933, when he still continued to complain of shoulder pain but of diminished intensity. When seen August 27, 1933, the pain had disappeared. On October 16, 1933, there was another attack of coronary occlusion with infarction of the posterior wall of the left ventricle. This attack was not followed by shoulder pain. Death occurred suddenly on August 25, 1935.

Extensive ancient infarction of both anterior and posterior walls of the left ventricle was found at necropsy.

CASE 8.—E. Q., a white female, aged 53, had been known to have hypertension for 13 years. In 1930 she suffered a severe attack of pain in the arms followed by unconsciousness. Coronary occlusion was suspected, but an electrocardiogram made several months later by one of us (C. C. W.) was normal. Another tracing made in 1932 showed minor changes but no evidence of myocardial infarction. On August 25, 1933, there was an attack of violent pain in the left shoulder region radiating to the neck and down the left arm to the finger tips. A tracing made 4 months later showed the healed stage of infarction of the anterior wall of the left ventricle. Following this violent attack, she was subject to attacks of angina pectoris provoked by exertion and relieved by nitroglycerin. The pain which began August 25, 1933, according to the patient, never disappeared entirely. Furthermore, the radiation to the neck and down the left arm to the finger tips persisted. This pain was considerably aggravated by her attacks of angina pectoris. Various types of medication appeared to be without effect on the shoulder pain, although as stated above, the angina pectoris was promptly relieved by nitroglycerin. Roentgen ray of the cervical spine and left shoulder, November 8, 1934, showed "hypertrophic changes involving the anterior lip of the lower cervical vertebræ: the left shoulder was negative." Death occurred suddenly on January 21, 1935.

CASE 9.—B. D., a white female, aged 58, was admitted to this hospital (service of Dr. Stengel) on March 25, 1934, 2 days after the onset of a severe attack of coronary occlusion. The acute pain was chiefly in the epigastric region. The electrocardiogram showed evidence of recent infarction of the anterior type. Her Wassermann reaction was positive. In addition to the regimen for the treatment of acute coronary occlusion, mercury and iodids were given. Her course in the hospital for a time was stormy, due to pain and congestive failure. By the early part of June these had cleared up. In the latter part of June, however, she developed pain in the right deltoid muscle which gradually shifted to the right shoulder region. From here the pain radiated to the bend of the elbow and occasionally down to the finger tips. No tenderness was present except during times when the pain was exceedingly severe. She was seen again on October 13, 1934, at which time she felt fairly well except for the pain in the right shoulder. Roentgen ray examination showed bilateral cervical ribs.

She was readmitted to the hospital on November 21, 1934, in a state of acute shock. The legs were cold, blue and pulseless. Death occurred the same day. Autopsy revealed old and relatively recent areas of infarction of the anterior wall of the left ventricle and a large soft mural thrombus beneath one of these areas. A thrombus completely occluded both iliac vessels. Examination of the cervical ribs disclosed these to be small and apparently not exerting pressure upon the neighboring bloodvessels or nerves.

CASE 10.—H. K., a white male, aged 60, a coppersmith, was in good health until September 25, 1934, when he was seized while at work with a severe agonizing pain over the upper chest, radiating to both shoulders and down both arms to the finger tips. Relief followed several hypodermics of morphin but a sense of numbness remained in the little and ring fingers of his right hand. An electrocardiogram showed evidence of infarction involving the posterior wall of the left ventricle. Convalescence was uneventful except for the very frequent occurrence of "heartburn" not relieved by alkalis. On October 14, 1934, he began to have persistent pain in both shoulders (dull, aching), worse at night and slightly aggravated by motion. The numbness of the two fingers of the right hand persisted. Roentgen ray of the spine and shoulders, taken November 19, 1934, dis-

closed no abnormalities in the cervical and upper dorsal spine or shoulders. Deep Roentgen ray therapy over the upper spine and shoulder instituted November 27, 1934, was without beneficial results.

Case 11.—L. U., a white male, aged 61, was first seen August 5, 1933. He had been in good health until 3 weeks before, when he experienced substernal pain following a large meal. He then improved rapidly, but on August 1, 1933, was seized with a severe substernal pain which radiated to the right shoulder and down the arm, for which he received 3 hypodermics. When seen on August 5, 1933, he was free from pain but felt very weak. An electrocardiogram showed recent infarction of the anterior wall of the left ventricle. He was ordered to bed and remained there 6 weeks, during which time convalescence was uneventful. However, toward the end of his stay in bed, he complained of a slight, constant pain in the right shoulder. On arising from bed this pain became more severe and radiated down the arm to the finger tips. Substernal pain radiating to the right shoulder also occurred often, especially on exertion or dietary indiscretion. He was seen at frequent intervals until March 13, 1934, but in spite of medication, rest and baking, the shoulder pain continued. The pain gradually subsided and on April 21, 1934, had disappeared. The attacks of substernal pain had also decreased in frequency and severity. Death occurred suddenly on January 5, 1935.

Case 12.—C. S., a white male, aged 56, was first seen March, 1933. He had suffered attacks of pain in the epigastric region for several years, especially on exertion or excitement. Following business reverses the attacks became more frequent and severe. On March 6, 1933, he was suddenly seized with a severe, agonizing, crushing pain in the upper sternum, radiating down both arms, but especially the left. An electrocardiogram showed evidence of recent infarction involving the anterior wall of the left ventricle. Following the initial pain, convalescence was uneventful until 4 weeks after the onset, when he developed a severe pain in the left shoulder radiating down the arm. The pain was constant, dull, aching and worse at night. Local applications, analgesics and baking failed to give appreciable relief. Roentgen ray of the teeth revealed one abscessed tooth which was subsequently removed. Following the extraction there was no immediate increase or decrease in the intensity of the pain. Four weeks later, or approximately 10 weeks after the onset of the shoulder pain, it decreased in intensity and gradually subsided.

Case 13.—H. W., a white male, aged 38, an insurance agent, was well until October 29, 1934, when he developed substernal pain radiating to both arms on effort and relieved by rest. The attacks increased in severity and intensity and on November 10 he had a very severe attack while at rest. He was put to bed and on the 4th day, upon arising from bed, he coughed up about 1 ounce of blood-tinged sputum. He was admitted to this hospital (service of Dr. Stengel) November 14, 1934, complaining of a constant, dull pain under the sternum. An electrocardiogram done November 16, 1934, was of the type found in the subacute stage of infarction involving the anterior wall of the left ventricle. Subsequent electrocardiograms showed huge *T* waves in Leads IV and V. Convalescence was uneventful and he was discharged from the hospital January 25, 1935. He was readmitted April 29, 1935. During the interim he had anginal pain and dyspnea on effort. Five weeks before his second admission he began to experience a constant "hot" pain in the right shoulder region made worse by movement of the shoulder, but not aggravated by exertion which did not involve movement of the right shoulder. On this admission he remained in the hospital only a few days. The pain was not relieved at the time of his discharge.

TABLE 1.—MYOCARDIAL INFARCTION AND SHOULDER PAIN.

Case.	Sex.	Age.	Location of infarct.	Shoulder affected.	Time relation of cardiac attack and onset of shoulder pain.	Duration of shoulder pain.	Anginal attacks.	Remarks.
1. P. M.	M	52	Anterior	Left	Less than 25 days	18 months; severity decreased	Severe	"Trigger zone" over upper left scapular region.
2. S. S.	M	62	Posterior	Left	4 months	5 years; no relief	Severe	"Trigger zone" over upper left scapular region; pain worse after attacks of angina.
3. D. S.	M	55	Posterior	Left	Coincident	Over 9 months; complete relief	?	Pain worse during and after attacks of paroxysmal dyspnea.
4. M. L.	M	58	Anterior	Left (biceps)	3 months	10 months; complete relief	No	Shoulder pain increased by excitement or cough; relieved following deep Roentgen ray therapy.
5. W. F. A.	M	48	Posterior	Both	Within a week	Approximately 8 months; no relief	Yes	Pain shifted from left to right shoulder.
6. W. J. R.	M	44	Anterior	Left	Coincident	2 months; no relief	No	
7. S. S.	M	58	Anterior	Both	Approximately 2 weeks	Approximately 1 year; complete relief; sudden death 2 years later	Yes	Posterior infarction over a year after anterior, not followed by shoulder pain.
8. E. Q.	F	53	Anterior	Left	Coincident	17 months; slight relief; sudden death	Yes	Aggravated by excitement; relieved by rest.
9. B. D.	F	58	Anterior	Right	4 months	Until death 5 months later	No	Bilateral cervical ribs; at necropsy found very small and exerting no pressure.
10. H. K.	M	60	Posterior	Both	4 weeks	4 months; no relief	No	Numbness in first and second fingers of right hand.
11. L. U.	M	61	Anterior	Right	Approximately 6 weeks	7 months; complete relief	Mild	Sudden death 8½ months after relief of pain.
12. C. S.	M	56	Anterior	Left	5 weeks	10 weeks; complete relief	Mild	
13. H. W.	M	38	Anterior	Right	4 months	6 weeks; no relief	Mild	
14. S. S.	M	53	Anterior	Left (deltoid)	6 weeks	7 weeks; complete relief	Mild	Pain never severe.

CASE 14.—S. S., a white male, aged 53, was referred for study on April 19, 1935. During the preceding 2 weeks he had noted several transient attacks of substernal pain. On the night of April 17, 1935, he was awakened by severe substernal pain, radiating down the left arm. Following the administration of morphin hypodermically by his physician the pain was relieved but not entirely abolished. Slight pain was still present on April 19, 1935. An electrocardiogram revealed the presence of acute infarction of the anterior wall of the left ventricle. He was kept at complete rest for about 7 weeks during which time there were several transient attacks of substernal pain. About June 1, 1935, he began to note pain in the region of the left deltoid muscle which persisted until about July 20. The pain was not severe but was constant. It did not interfere with movement of the left arm and was not aggravated by movement. There was no tenderness over the deltoid nor shoulder region and no limitation of motion. No sensory changes were noted.

Discussion. *Incidence.* Persistent pain in the should region following myocardial infarction is apparently not an uncommon symptom. However, we were unaware of this relationship until several patients, all of whom had had myocardial infarction, complained bitterly of shoulder pain. Our failure to account for the pain on any conventional basis led to consideration of the possibility that the cardiac lesion might in some way be responsible. For this reason a systematic study of our other available patients who had survived attacks of infarction was made, and a total of 14 cases with persistent shoulder pain was assembled. In all, approximately 100 cases were followed, which suggests that the incidence of this symptom among the survivors of attacks may be over 10%.

The sex, age, location of the infarct (as determined by electrocardiogram), the time of onset of shoulder pain with reference to the acute attack of infarction, the duration of the shoulder pain, the presence or absence of anginal attacks and certain atypical features of the various cases are listed in Table 1.

Character of the Pain. The pain has been described as "burning," "aching," or "wrenching." As a rule the patients had some difficulty in localizing it, often referring it to the general region of the shoulder. In 1 patient, however, the pain was limited to the region of the left deltoid muscle and in another, was greatest over the biceps. In 8, the pain was limited to the left shoulder region, in 3, to the right, while in 3 both shoulders were affected. The pain tended to be continuous, although subject to periods of exacerbation and amelioration. In 2 patients there was a so-called "trigger zone" in the scapular region, pressure over which caused great increase in pain. Those who suffered attacks of angina pectoris had no difficulty in distinguishing them from the shoulder pain, but in a few, the shoulder pain was definitely worse following an attack of angina. In 1 case the shoulder pain was increased during and immediately after attacks of paroxysmal dyspnea.

Time Relation to Acute Cardiac Attacks. The time of onset of the shoulder pain was variable. In 3 of the 14 cases it appeared

to be practically coincidental with the attack of coronary occlusion. The longest interval between occlusion and shoulder pain was 16 weeks after the attack. In a number of cases the pain came on so gradually that the patient could not date it accurately. In all but 4, however, it began within 6 weeks of the attack.

Duration. The duration of the pain in this series of cases varied greatly. In 1 case it was mild and lasted only 7 weeks. At the other extreme is the case in which the pain has persisted for 5 years and still continues. In 6 of the patients pain was still present at the last follow-up examination. Two of the 4 patients who died continued having shoulder pain up to the time of death. Six were relieved of the pain in periods varying from 7 weeks to 12 months.

Possible Non-cardiac Causes. 1. Results of Physical Examination: In most of these patients, physical examination of the shoulder region has proven entirely negative. As a rule, ordinary movement does not aggravate the pain, but in a few patients, pain seemed to be increased by exaggerated movements of the shoulder. Except for the 2 patients with so-called "trigger zones" over the back of the shoulder, no tenderness on pressure was elicited in the region of the shoulder, arm or back. There appeared to be no impairment of strength of the shoulder muscles, no atrophy, and no sensory changes. No vasomotor changes were noted and no differences in the pulses on the two sides were found. The occurrence of periarthritis of the shoulder, in cases with cardiac pain, has been reported by Howard.[1] We were, however, unable to find evidence of periarthritis in any of our cases.

2. Roentgen Ray Examinations: Roentgen ray studies of the shoulders and spine were made in 7 of the more severe cases. In 6 the shoulders were entirely negative. In 1 there was a slight calcareous deposit in the right subacromial region, but the left, which was the painful shoulder, showed no abnormality on Roentgen ray examination. In 3 cases slight lipping of the bodies of the vertebræ was found, not sufficient to be considered abnormal for this age group. In 1 case, however, Roentgen ray of the chest disclosed bilateral cervical ribs, but at necropsy these were found to be quite small and apparently incapable of exerting pressure on neighboring bloodvessels or nerve trunks.

Results of Treatment. Treatment for the relief of pain was singularly ineffective. The ordinary analgesics (not including opiates), nitrites, baking, diathermy and removal of foci of infection appeared to be without material influence. In 1 case deep Roentgen ray therapy seemed to relieve pain; in 1 it gave a questionable result, but in 2 others it was ineffective.

Analogy of the Pain to Causalgia. The time relations of the onset of pain to attacks of coronary occlusion, and its peculiar characteristics, which tend to differentiate it from the well recognized forms of shoulder pain, suggest that it is related to the cardiac lesion and referred from the heart. It should be stated, however,

that in most cases there was recognized no significant correspondence in location between stenocardiac types of pain and the shoulder pain. In a few cases, however, there did appear to be some correspondence.

It occurred to us that the shoulder pain bears a closer analogy to causalgia than any other recognized type of pain, although the trophic and vasomotor changes associated with causalgia have not been observed in our cases. Furthermore, hyperesthesia was present in only 2 cases.

Pollock and Davis[2] have recently stated that the pathogenesis as well as the pathology of causalgia is unknown. These authors, however, associate causalgia with peripheral nerve injuries. Leriche[3] believes that periarterial sympathetics play an important part in the production of causalgia and that such lesions as obliteration of an artery or inclusion of sympathetic fibers in a scar may provoke the syndrome. In support of his hypothesis he has been able to bring about complete relief in most of his cases by periarterial sympathectomy. In some cases, however, it was necessary to resect the obliterated artery in order to obtain relief.

Whether or not under the term causalgia more than one entity is included need not concern us here. Our interest is in the fact apparently demonstrated by Leriche that obliteration of an artery may cause causalgia. Leriche's studies have dealt with peripheral arteries. However, the characteristics of the shoulder pain as it occurred in our patients as well as its refractoriness to treatment bear such a close analogy to the pains which may develop after block of a peripheral artery that a similar mechanism of pain production is suggested. No additional evidence is available at present to support this view. The operation of cervico-thoracic sympathectomy might throw some light on the question as to whether the sympathetics are concerned in production of the pain. However, we have not thus far felt warranted in suggesting this operation to any of our patients. Consequently the analogy of the pain to causalgia is suggested for the following reasons only: (1) the similarity of the pain to causalgia and (2) the time relationship of onset of the pain to occlusion of a coronary artery. The chief purpose of this report is not to discuss the pathogenesis of the pain, but rather to call attention to the fact that it is to be recognized as a sequel to coronary occlusion.

Although this study has been limited to a consideration of cases in which shoulder pain developed following myocardial infarction, there is some evidence to indicate that a broader relationship may exist. Thus, since we have become interested in this subject, we have encountered 1 patient with persistent burning pain in the interscapular region and another with a persistent sensation of warmth and at times burning in the left forearm, following coronary occlusion. Moreover, shoulder pain of the type described above has occasionally been complained of by patients with severe myo-

cardial damage, in whom no evidence of infarction could be recognized.

Summary. 1. Fourteen cases with persistent pain in the shoulder region following myocardial infarction have been briefly described. It is suggested that the incidence of this symptom among survivors from infarction may exceed 10%.

2. The pain may be mild or severe and was usually described as burning, aching or wrenching. The left shoulder is usually involved, although the right may also be affected. The pain may shift from one shoulder to the other. Occasionally the pain may be greatest in the region of the biceps or deltoid muscles.

3. It may begin coincidentally with an attack of coronary occlusion up to at least 16 weeks after the attack.

4. The pain persisted from 7 weeks to over 5 years.

5. Local treatment to the shoulder has proven ineffective. Deep Roentgen ray therapy has been tried in several cases without consistent results.

6. Most patients in this group had foci of infection. A few had slight cervical or upper dorsal spondylitis. Nevertheless, the frequency of occurrence after myocardial infarction and the time relations to the attacks, suggest that the cardiac lesion is an important etiologic factor. An analogy to causalgia is suggested.

REFERENCES.

1. Howard, T.: Cardiac Pain and Periarthritis of the Shoulder, Med. J. and Rec., **31**, 364, 1930.

2. Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries, Am. J. Surg., N.S. **15**, 395, 1932.

3. Leriche, D.: De la sympathectomie peri-arterielle et de ses resultats, Presse méd., **25**, 513, 1917. Leriche, R., and Stricker, P.: L'arteriectomie dans les arterites obliterantes, Masson et Cie, Paris, 1933.

ACETYL β METHYLCHOLIN.

IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm.

By Isaac Starr, Jr., M.D.,

Hartzell Professor of Research Therapeutics, Hospital of the University of Pennsylvania, Philadelphia, Pa.

(From the Research Department of Therapeutics.)

Many derivatives of cholin, administered to animal preparations, produce effects on the heart analogous to those which follow stimulation of the vagus.* [19] By means of acetyl-β-methylcholin this

* Since 1925 paroxysmal tachycardia has been occasionally stopped by intravenous injections of cholin chlorid (Bohnenkamp, Klin. Wchnschr, **14**, 404, 1935). Stepp and Schliephake (Münch. med. Wchnschr, **72**, 1997, 1925) also reported a case of "paroxysmal tachycardia" in which unnamed "cholin derivatives" caused increased block. The ekg. given suggests auricular flutter.

effect can be produced in the clinic to a degree not yet attained by other means. The therapeutic utility of the cardiac action of this drug will be considered in this paper. The drug also produces the other effects of parasympathetic stimulation: vasodilatation, saliva-

Both Professor Hunt[10] and Professor Villaret[11] and their associates had published animal experiments in which a drug was employed under the name of acetyl-α-methylcholin. That this drug had been erroneously named did not occur to us in 1933.

Following Simonart's publication,[12] Hunt took the position that what he had described as acetyl-α-methylcholin was in reality acetyl-β-methylcholin.[13,20] Professor Villaret[14] suspected that what he had used might have been a mixture of acetyl-α- and acetyl-β-methylcholins. The latter view is concurred in by Simonart,[16] who finds acetyl-α-methylcholin to be a much weaker drug than the β compound. Later Villaret adopted Hunt's point of view.[15]

After using what he then believed to be a mixture, in 1932, Villaret *et al.*[14] published an article, entitled "Preliminary Researches Concerning the Action of Methyl Acetyl Cholin in Normal Subjects." This antedated our first publication, reaching our attention when it was in press. After doses of 10 to 30 mg. of the bromid, Villaret recorded flushing and effects on the blood pressure of 12 normal subjects which corresponded in a general way with results we obtained using the acetyl-β-methylcholin chlorid made by Major and Cline's method. But the absence of any record of sweating, of salivation and of changes in cardiac rate and respiratory depth, so conspicuous after similar doses in our experiments, made us doubt whether the drug used by Villaret, made by Morley's method, could have been the same as that we employed, made by the method of Major and Cline. A further difference in results seemed to be indicated by the following statement: "Nous avons établi qu'en installations conjonctivales la méthylacétylcholine déterminait rapidement un myosis intense, et que, fait très intéressant, seule entre tous les myotiques actuellement connus, elle arrivait à vaincre aisément la dilatation pupillaire provoquée par l'éphédrine. In another paper,[21] speaking of the action of 1 or 2 drops of the misnamed acetyl-α-methylcholin in the rabbit's eye he wrote: "Il faut, cependant, utiliser les concentrations de l'ordre de 5 p. 100, ou, mieux encore, de 10 p. 100, pour voir apparaître, en deux à quatre minutes, un myosis qui est maximum en quatre à sept minutes, avec pupille réduite à un orifice de 1 millimètre environ; cet effet commence à diminuer après 45 à 60 minutes, pour persister, atténué, jusqu'à deux heures après l'instillation."

Hunt obtained similar results with his misnamed acetyl-α-methylcholin on the pupils of dogs and cats. He wrote: "One drop of a 3% solution caused an intense constriction within 5 to 10 minutes; this continued undiminished for about 15 minutes."[10]

I have repeated these experiments as closely as possible with Major's acetyl-β-methylcholin chlorid. In 3 brown rabbits slight pupillary constriction was always seen after 1 or 2 drops of 10% solution. In the most striking experiment the pupil diminished from 6 to 4 mm. diameter and so became 2 mm. smaller than the opposite pupil. In 3 white rabbits 2 drops of 10% caused the pupil to diminish from 10 to 8.5 mm. in one animal, it had less effect in the other two, although enough was absorbed to cause salivation in each instance.

Dr. Schmidt has failed to obtain myosis in cats using repeated applications of 1%,[16] and I could not demonstrate noteworthy myosis after 1 drop of 3% in three cats.

When stronger solutions are applied to the conjunction with sufficient frequency some myosis can be regularly obtained together with evidence of systemic action. But we have never seen anything which is at all similar to the effects described by Hunt and by Villaret after the doses they employed. But it should be pointed out that we have not repeated the experiments of the latter author, for the European rabbit differs from the American.

The drug used by Hunt and by Villaret in these early experiments was described as a "unique" myotic causing "intense constriction" after small doses. Pure acetyl-β-methylcholin has only a weak myotic action; marked pupillary effects have not been seen without increasing the dosage to the point of inducing systemic effects. There is also chemical and other pharmacologic evidence that the two were not identical.[16, 17] But that Hunt and Villaret were employing an active cholin derivative with features in common with acetyl-β-methylcholin is not disputed.

tion, sweating, increased gastro-intestinal motility, etc., as have been described.[1] When small doses are given to animals and to normal persons the blood pressure falls but the vagus-like action does not manifest itself. After large doses this effect appears.[2] It cannot be produced without the simultaneous occurrence of a fall in blood pressure and the other effects mentioned above to such a degree that the subject is made distinctly uncomfortable for a few minutes. However, after a subcutaneous injection of acetyl-β-methylcholin, the intensity of the action remains under the control of the attending physician. This fact has made possible the utilization of a type of drug action more vigorous than is usual in clinical medicine.

In an earlier communication[2] (1933) the results obtained in the treatment of 29 attacks of paroxysmal tachycardia in 9 patients were reported. At present, data are available on 75 such attacks, in 36 patients, treated by acetyl-β-methylcholin with success in 88%. Six cases of auricular flutter have also been treated, but with only occasional success in restoring normal rhythm. In 1 case with ventricular extrasystoles the number of premature beats was markedly reduced by the drug. In auricular fibrillation no change in the rhythm has been brought about.

Additional clinical experience has added to our knowledge of the drug and has afforded an explanation for some of the failures reported. One can now draw a clearer picture of the best method of securing results with acetyl-β-methylcholin in the cardiac arrhythmias, of its probable effectiveness when thus employed, and of its untoward effects, than was possible a few years ago.

Paroxysmal Auricular or Supraventricular Tachycardia. Electrocardiograms demonstrating the arrhythmia to be of this type were secured in only 20 of the 37 patients, but clinical criteria permitted little doubt that the attacks of the remainder were of the same type. These data (Table 1) can be considered best by dividing them into

TABLE 1.—DATA ON EFFECT OF ACETYL-β-METHYLCHOLIN ON PAROXYSMAL TACHYCARDIA.

	Philadelphia.	Other.	Total.
Number of patients	17	20	37
Attacks treated	50	25	75
Attacks stopped	46	20	66
Failures	4	5	9
Per cent success	92	80	88
Successful from drug action alone on first trial	58%		
Required carotid sinus pressure during drug's action	20%		
Required second, usually larger, dose of drug	22%		

two groups: The Philadelphia group contains my own experience together with a small number of other cases treated at the University Hospital in my absence but in accordance with a plan I devised.

This is a selected group because carotid sinus pressure failed to stop the attack in each case included. The second group contains data sent me by friends in other cities. I am especially indebted to Dr. H. M. Korns, of Iowa City, Dr. J. M. Hayman, of Cleveland, Dr. H. M. Marvin, of New Haven, and Dr. D. N. Kremer and Dr. F. W. Burge, of Philadelphia, for very full reports of their experiences. The attacks of many patients in this group could not be stopped by carotid pressure, but in others this was not tried, and in a few instances I lack the information.

The Philadelphia cases were treated as follows. The patients lay down. Alternate pressure over the carotid sinuses was tried first. This was successful in 16 instances, and these cases have been eliminated from this study. When carotid sinus pressure was unsuccessful the drug* was given subcutaneously. If the attack did not stop promptly after the appearance of the flush, the site of the injection was vigorously massaged to increase the action. In 26 instances (58%) the attack was brought to an end by these means alone. If tachycardia persisted, the carotid sinuses were compressed alternately while the action of the drug was still undiminished. Frequently the attack stopped as soon as one of the sinuses was touched. In 9 instances (18%) the attack was terminated by carotid pressure during the drug's action, although similar pressure before its administration had been ineffective.

If tachycardia still persisted, about ½ hour was allowed for the drug's effects to subside. Then a second, usually a larger, dose was given, and the procedure repeated. The second attempt was successful in 10 cases (22%). But this does not mean that one should expect the first attempt to fail in a corresponding number of cases. For, in order to estimate the smallest effective dose, we often purposely gave an initial dose so small that there was little expectation of success.

In 4 instances we failed to effect a prolonged restoration of normal rhythm, and I have information concerning 5 other failures. Before the reason for these failures can be discussed profitably, certain information derived from the data must be considered.

Relation of Dose to Age and Weight. The first study suggested that 30 mg. was the proper dose for paroxysmal tachycardia. A dose of this size has been successful in patients under 52 years, but it has failed more often than it has succeeded in older patients Fig. 1). In a boy, aged 18, the attack was stopped by 10 mg., and the side effects were just as intense as those which followed the injection of the 50 mg. regularly required to stop attacks in a man aged 60.

The line drawn on Fig. 1 gives a rough idea of the dose which experience indicates may be expected to stop tachycardia at different

* We are indebted to Merck & Co. for supplying the acetyl-β-methylcholin chlorid used.

ages in patients of normal weight. Some of the most divergent points can be explained on the basis of unusual weight, *e. g.*, 60 mg. was required for an extremely fat man aged 42; 20 mg. was successful in a thin woman aged 58. Other divergent points may have been due to poor selection of dosage. Thus, in 2 instances, young people were given 30 and 35 mg. with success; we do not know that smaller doses would not have been equally effective.

Obviously larger doses are usually required in older people than in young ones. It is incorrect to assign a single dose for all cases

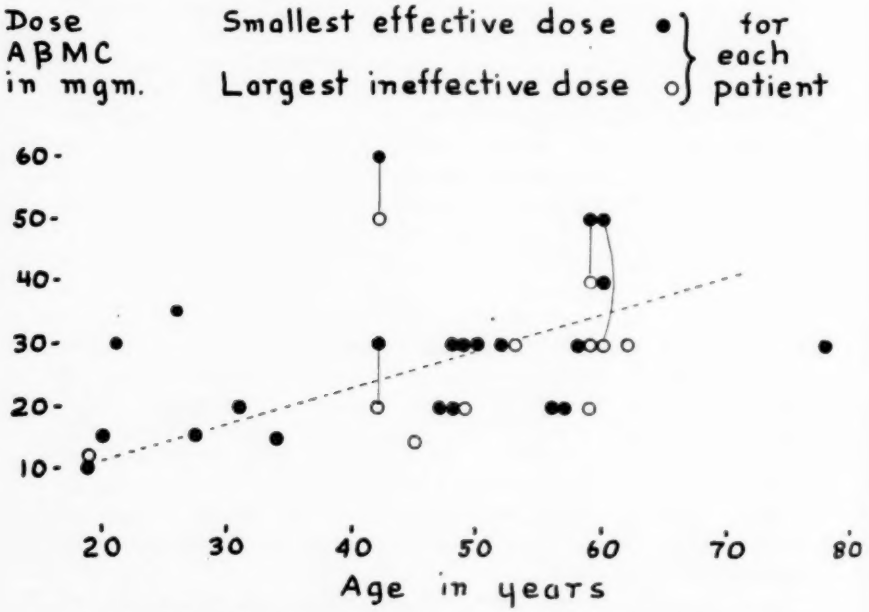

FIG. 1.—Effect of age on the dose of acetyl-β-methylcholin necessary to stop attacks of paroxysmal tachycardia. Only the *largest dose which failed* to stop an attack and the *smallest dose which succeeded* in any 1 patient have been given. Two points which apply to the same patient have been connected by lines. In many cases one or the other of these points is unknown.

of paroxysmal tachycardia. That young persons react to the drug more vigorously than older ones has been the experience of Page[3] also.

Antagonism Between Cardiac Action of Acetyl-β-Methylcholin and Quinidin. The latter drug is well known to diminish the frequency of attacks of paroxysmal tachycardia in certain cases, though it has no reputation as an agent to bring such attacks to an end. Therefore, it appeared worthwhile to ascertain whether a combination of the two drugs' actions might not be advantageous in stopping attacks.

Soon after this idea had presented itself, a patient appeared in tachycardia whose previous attack had been promptly brought to an end by an injection of 30 mg. of acetyl-β-methylcholin. I gave him 20 mg., expecting that it would prove too little, without affecting the rhythm. He was then given 0.67 gm. quinidin by mouth; this was followed by a glass of water, and he was instructed to lie on his right side; a procedure which has regularly procured quinidin action within ½ hour, in my experience. This time having elapsed, the patient received a second dose of 20 mg. acetyl-β-methylcholin in the hope that, reinforced by the quinidin, it might stop the attack. It failed to do so. Doses of 30 and, later, 50 mg. acetyl-β-methylcholin failed also, although they produced the usual side effects. Therefore, the outcome suggested that, far from making the attack easier to stop, quinidin antagonized the usual cardiac effect of acetyl-β-methylcholin.

The opportunity to repeat a clinical observation of this type coming but rarely, it seemed wise to investigate the relationship between the cardiac effects of quinidin and acetyl-β-methylcholin in animal experiments. The results indicated that an antagonism between the cardiac effects of these two drugs could be easily demonstrated.[4]

On the other hand, in 5 instances, patients receiving small doses of quinidin, the largest 0.2 gm., 4 times a day, have had attacks successfully stopped by acetyl-β-methylcholin. The cardiac action of large doses of acetyl-β-methylcholin will break through the quinidin block both in the clinic and in animal experiments.

Causes of Failure to Stop Attacks of Paroxysmal Tachycardia. The chief cause of failure has been too small dosage of acetyl-β-methylcholin. In 10 attacks, in 4 patients, this was proved to be the case when a second and larger dose, given after the effect of the first had subsided, was immediately successful. In 2 instances, both early in our experience and mentioned before, we did not increase the dose and failed to bring the attack to an end. One of these, a patient with ulcerative colitis, received only 12 mg. He vomited and defecated after this dose, and the physician in charge did not try a larger one. As other attacks were stopped by 15 and 20 mg., the failure mentioned is to be attributed to inadequate dosage. In 2 patients, treated in another city by doses of 20 mg., the failure is probably to be assigned to the same reason. Dosage of this size will seldom stop attacks in the latter half of life.

In 3 instances the failure may be assigned to previous medication with quinidin. One patient, given quinidin experimentally, has been discussed above. Another of our patients (C. M. K.) had received 0.5 gm. quinidin and 1 gm. digitalis before treatment with acetyl-β-methylcholin. But we did not give over 15 mg. of the latter drug, which caused transient complete block without stopping the attack. The failure might be assigned to inadequate dosage for

his age, to quinidin, or to an unknown factor. He had received too many active drugs to permit accurate analysis. Complete block, lasting over a few beats, has never been produced in any other of our patients.

In a case of Dr. H. M. Marvin, the patient had been taking 0.6 gm. quinidin sulphate, 3 times a day, for many months. She had taken 2 such doses the morning of the attack, and it was not stopped by 30 mg. of acetyl-β-methylcholin. The quinidin may certainly have been the cause of failure in this instance.

One case of my own and 2 other cases still lack a clear reason for failure. The former deserves brief mention.

A young girl, aged 22, came to me with the history that she had an attack of tachycardia whenever a young man invited her to go to a dance. The attack in which she presented herself was attributed to this cause. The electrocardiogram showed it to be of the supraventricular type. During the action of 20 mg. acetyl-β-methylcholin the attack stopped, as judged by heart sounds, but it resumed promptly. While the drug's action continued, it could be stopped immediately by carotid sinus pressure on either side and by having the patient take a deep breath and hold it; but the rhythm always reverted to tachycardia within ½ minute. A second and third dose of 25 mg. had the same effect. The attack stopped at least 20 times, but it always resumed within a minute; so I admitted defeat eventually. It stopped spontaneously 10 hours later, at almost the exact time the dance was over. I have no explanation of the failure other than to point out my inability to remove the cause of the attacks in this instance.

Attempts to Stop Attacks of Paroxysmal Tachycardia by Other Methods. Seeking for a better method of stopping attacks, I have tried, unsuccessfully, an injection of 30 mg. of the ethyl ether of β-methylcholin and, in another instance, 0.5 mg. of carbaminoylcholin (doryl or lentin). Trying to minimize the side effects I having given an adequate dose of acetyl-β-methylcholin dissolved in ethyl lactate to slow the action, and I have injected the drug together with 0.6 mg. atropin. The side effects were diminished in both cases, but the attacks were not stopped. In each instance, after allowing the effects of the injected drugs to subside, the attacks were promptly stopped by acetyl-β-methylcholin, given in the usual manner.

Dr. Korns has informed me that he successfully stopped an attack of paroxysmal tachycardia by an intravenous injection of 20 mg. acetyl-β-methylcholin without undue toxic effects. The patient's condition, carcinoma of the throat, justified the risk taken.

Auricular Flutter. I have data on only 6 cases of this arrhythmia who were given the drug on 12 occasions. Four cases were my own, and in 3 electrocardiograms were secured throughout the drug's action. I am indebted to Dr. Korns for permission to mention his experience in 2 others.

Temporary slowing of the ventricular rate was secured in all 6 cases by large doses of the drug, 60, 40 or 30 mg. The electrocardiogram showed the slowing to be due to increased block.

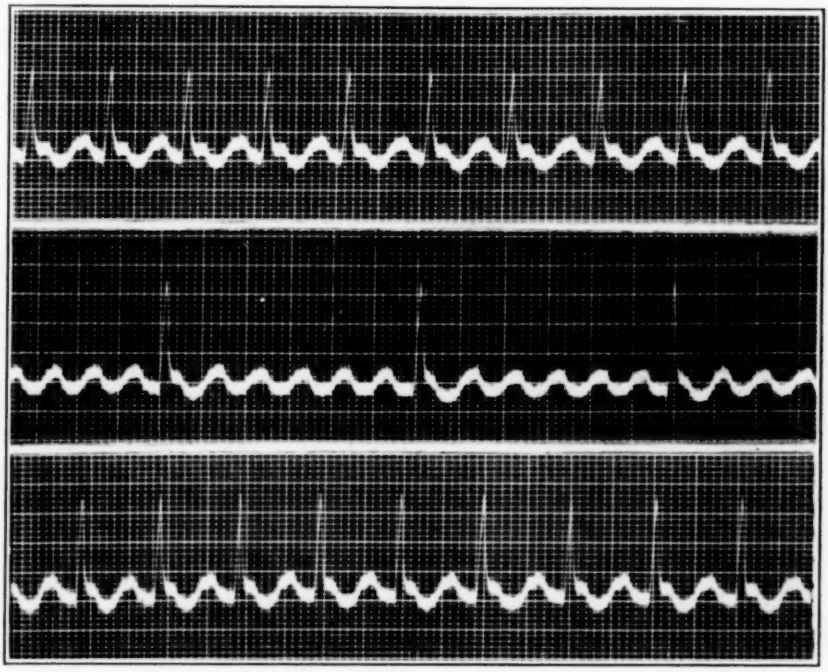

FIG. 2.—Effect of acetyl-β-methylcholin on auricular flutter. Lead II: The upper tracing was taken before, the middle 2 minutes after, the lower 25 minutes after the subcutaneous injection of 44 mg. acetyl-β-methylcholin.

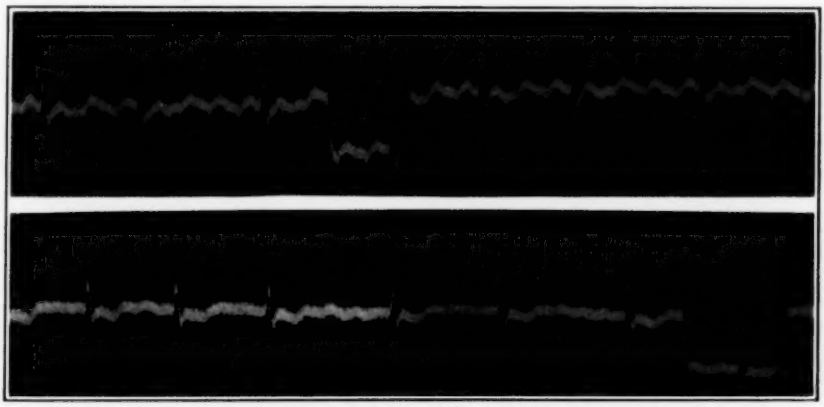

FIG. 3.—Effect of acetyl-β-methylcholin on auricular flutter. Lead II: The upper tracing was taken 2 minutes before, the lower 4½ minutes after a subcutaneous injection of 40 mg. acetyl-β-methylcholin. The patient was under the influence of digitalis.

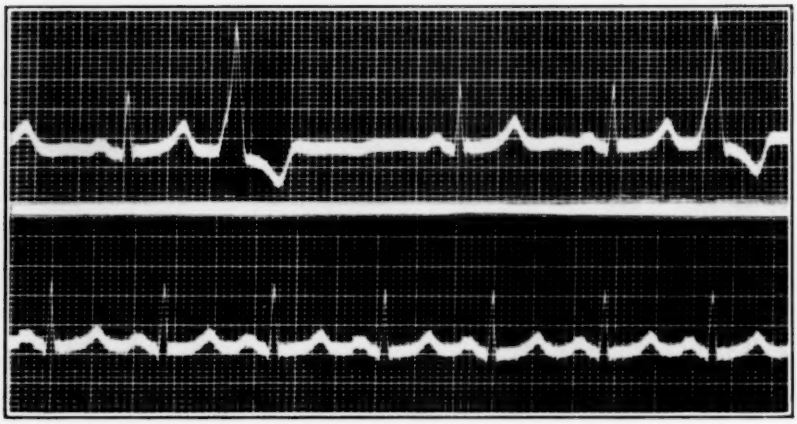

FIG. 4.—Effect of acetyl-β-methylcholin on ventricular extrasystoles. Lead II: The upper tracing was taken 2 minutes before, the lower 5 minutes after a subcutaneous injection of 20 mg. acetyl-β-methylcholin.

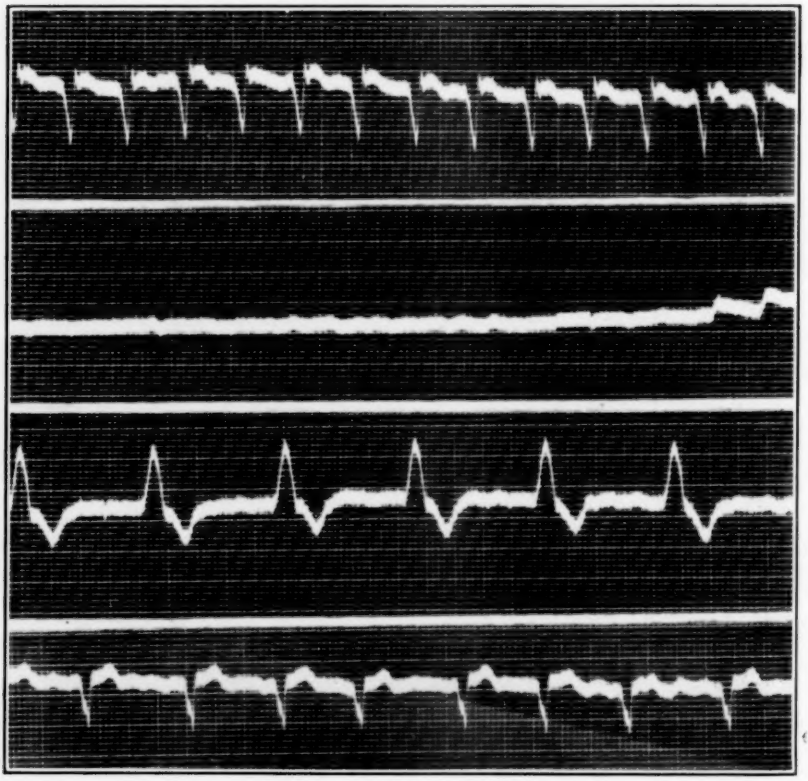

FIG. 5.—Effect of a toxic dose of acetyl-β-methylcholin, 30 mg., *intravenously*. Lead II: The upper tracing was taken before the injection, the second is typical of the record obtained during the next 70 seconds. The third and fourth show successive phases of recovery.

Figure 2 shows such an effect. After the drug's action had passed off the original rate was resumed. Change in the auricular rate was not recorded except in the case mentioned below.

More permanent effects were seen in 2 instances. One patient, with advanced rheumatic heart disease and congestive failure, was given 30 mg. The auricular rate remained constant at 226. The ventricular rate changed from 100 to 120, then to 114; the relation between the adjacent *P* and *Q* waves, inconstant before the drug, became fixed after it at 2 to 1 block. She was then placed on digitalis, without alteration in the flutter, until nausea and vomiting forced us to withdraw the drug 10 days later. Two days after this she was given 40 mg. acetyl-β-methylcholin, and during the action the auricular rate rose from 230 to 300 and then the rhythm changed to auricular fibrillation (Fig. 3). Digitalis was withheld and fibrillation was succeeded by normal rhythm 4 days later. This gratifying result did not produce the expected clinical improvement. Not long afterward the patient developed a hemiplegia and eventually died. Necropsy was not permitted.

Nahum and Hoff[22] have reported a case similarly converted from flutter to fibrillation. Their patient was also under the influence of digitalis when acetyl-β-methylcholin was given. Normal rhythm returned 1½ hours later.

Dr. Korns converted 1 of his cases from flutter to normal rhythm by a dose of 50 mg. acetyl-β-methylcholin. Whether the heart went through fibrillation is unknown. Six months later the same patient had another attack. Four injections, ranging from 40 to 60 mg., had no effect on the auricular flutter in this instance. Normal rhythm returned spontaneously some hours after the last dose.

Auricular Fibrillation. No permanent effects have followed the administration of acetyl-β-methylcholin in this condition. A temporary effect, slowing of the ventricular rate, was seen in most instances, but seemed too transient to be of therapeutic importance. As restoration of normal rhythm was not expected from theoretical considerations, and as nothing of therapeutic importance was gained in the first 10 cases, we have not continued the study of this group.

Nahum and Hoff have produced transient auricular fibrillation by giving large doses to cases of thyrotoxicosis.[22]

Ventricular Extrasystoles. Only 1 case has appeared with extrasystoles in sufficient number to make a study possible.

The patient, an Italian male, aged 50, had many vague complaints for which no satisfactory diagnosis was ever suggested. On the first occasion he was having an extrasystole which replaced every third beat with perfect regularity. An electrocardiogram taken for 5 minutes showed no deviation. After an injection of 30 mg. acetyl-β-methylcholin the extrasystoles greatly diminished in frequency, large numbers of normal beats occurring between them (Fig. 4). They were never entirely abolished and no ½-minute

period occurred without an extrasystole. When the drug's action subsided the original condition returned.

The next day the extrasystoles were found to be replacing every fourth normal beat with perfect regularity. A dose of 70 mg. of the ethyl ether of β-methylcholin was given by mouth. Flushing, sweating and salivation appeared about 1 hour later. At this time the extrasystoles lost their regularity and occurred, on the average, at a ratio of 1 to 8 normal beats. Atropin sulphate, gr. $\frac{1}{150}$, subcutaneously, was given to abolish the cholin action, and within 3 minutes the extrasystoles returned to their original condition, replacing every fourth beat.

On another day the extrasystoles again replaced every third normal beat. The patient was given 1 gm. of acetyl-β-methylcholin, by mouth. Flushing and salivation appeared about $\frac{1}{2}$ hour later. At this time the extrasystoles had diminished to an average of of 1 to 5 normal beats. But on this occasion atropin did not entirely restore the original condition for, after its administration, while the extrasystoles usually replaced every third beat, occasional runs of 3 or 4 normal beats were heard.

Toxic Effects. The Effect of Overdosage. I have been permitted to cite certain instances when misunderstanding of orders resulted in overdosage.

A man, aged 71, had arteriosclerotic heart disease and auricular fibrillation; 30 mg. acetyl-β-methylcholin were administered *intravenously* instead of subcutaneously as directed (Fig. 5). The heart was arrested immediately and this persisted for 70 seconds, a fact of no little interest in itself. The patient lost consciousness. Atropin was administered. The ventricle resumed beating with evidence of an intraventricular conduction defect. The patient revived and within 20 minutes felt as well as before. The conduction defect soon disappeared, but the electrocardiogram remained very different from that present before the drug was given.

In another instance a man, aged 61, with auricular flutter, received 300 mg. subcutaneously instead of 30 mg. There was prolonged cardiac arrest and consciousness was lost. Atropin was administered, the heart resumed beating, and recovery was complete within a few minutes.

In both these instances the atropin could hardly have left the site of injection until cardiac action resumed. Therefore, initial recovery is not to be attributed to atropin, but rather to the well-known physiologic principle: vagus stimulation will stop the heart's action, but the heart will soon escape and resume beating even though stimulation is continued.

Cardiac Arrest Not Due to Overdosage. A situation quite similar to those mentioned above has occurred after a small dose of the drug under the following conditions.

Patient, W. S., aged 19, had ulcerative colitis and marked anemia as well as attacks of paroxysmal tachycardia. While in the hospital 3 attacks were stopped by doses of 10, 15 and 20 mg. acetyl-β-methylcholin. On

each occasion the patient had an irresistible defecation at the height of the action; a pan was provided so that he could remain lying down until action had subsided. After discharge he had another attack of tachycardia and the attending physician injected 10 mg. without provision for defecation. Therefore, when the action began, the patient leaped out of bed to go to the toilet, but soon after attaining the upright position he collapsed, and no heart sounds could be heard. The boy revived within a few minutes and there were no after effects. Atropin was not administered.

The physiologic explanation of this incident seems reasonably clear. Any drug or other situation which lowers blood pressure is likely to cause fainting if the subject is in the upright position. Part of the physiologic mechanism of the fainting reaction is analogous to the response to vagus stimulation; the heart is materially slowed or it may stop for a brief period.[5,6] In this incident the fall in blood pressure due to acetyl-β-methylcholin, together with the patient's lack of hemoglobin, caused cerebral anemia as soon as he took the upright position. The vagus-like effects of fainting and of the drug summated and caused cardiac arrest similar to that seen after gross overdosage.

Patients must be kept in the horizontal position during the action of acetyl-β-methylcholin.

Of the minor toxic manifestations, little has been encountered which was not mentioned in the previous communications,[1,2] but some additional information is at hand.

Asthmatic attacks promptly follow an injection of the drug in patients subject to this disease. This does not occur in other patients, but a sense of tightness across the chest is often complained of and is doubtless due to the bronchoconstrictor action demonstrated in animals by Comroe and Starr,[8] and its result, a decrease in vital capacity, demonstrated to occur in normal men by Hurtado and Kaltreider.[7] Villaret *et al.*[9] have made more extensive observations on this effect of the drug, producing typical attacks in 20 cases of asthma and in 1 patient, convalescent from pneumonia, who had never had asthma.

Substernal pain, or pain referred to the precordium, has followed the administration of the drug on rare occasions. The most striking examples of this were in 2 cases of advanced Buerger's disease with amputations for gangrene. In 1 of these, a patient of Dr. Kremer, it repeatedly followed the injection of 10 and 15 mg. I can only speculate as to its origin. The location of the pain and the well-known frequency of coronary sclerosis in organic peripheral vascular disease suggest that it might have arisen from the heart. But many other arteriosclerotic persons have received much larger doses of this drug without inducing this symptom.

The coronary action of acetyl-β-methylcholin is not identical in different preparations. In perfused isolated rabbit hearts the drug had usually only a slight effect on the coronary vessels. In 6 such preparations dilatation was regularly seen in 3, constriction pre-

dominated in 2, and there was no noteworthy effect in the other. In the cat, decreased flow was the rule after certain dosage, although mixed effects were sometimes seen.[8] Therefore, the animal experiments have not provided a firm basis for predicting how the drug acts on human coronary vessels.

Another possible explanation is spasm of the esophagus or cardia. I have seen a surprising increase of esophageal peristalsis under the fluoroscope after certain cholin derivatives. While I have never experienced precordial discomfort after an injection of acetyl-β-methylcholin, I have had a dull epigastric and substernal ache after taking another cholin derivative, doryl. This seemed to me to arise from the stomach.

This type of toxic response is very rare in its severe form. Dull precordial or substernal sensations, sometimes spoken of as pain, occur more frequently. Atropin relieves both types immediately, a fact which at once differentiates the drug effect from typical angina pectoris. Nevertheless it seems wise to use this active drug with caution in cases of angina pectoris until more data have been accumulated.

Nausea and vomiting occur occasionally after the drug. I think of them as being the first symptoms of overdosage. In most instances the full cardiac effect of the drug can be attained without these symptoms, but occasionally, as when the patient has recently been nauseated, they occur after moderate dosage.

On the Question of Chronic Toxicity. Nothing has appeared which suggests that harm may result from the prolonged use of this very active drug. In support of this statement it is desirable to report the case who has received a far larger amount of the drug subcutaneously than any other person.

T. H., an elevator operator, aged 58, in May, 1931, gave a history of attacks of paroxysmal tachycardia for 11 years. For the first 10 years he had usually been able to stop the attacks himself, but more recently he had lost this ability and they were increasing in frequency and duration. He denied dyspnea on exertion except during the attacks. Physical examination showed some cardiac enlargement, slight arteriosclerosis, dental and tonsilar infection. Basal metabolic rate was normal. Repeated electrocardiograms showed auricular tachycardia; when not in an attack the electrocardiogram was essentially negative. The cardiac area by orthodiagram was 43% above the predicted normal.

Throughout his illness he had frequently received quinidin, digitalis and phenobarbital in varying dosage in unsuccessful attempts to prevent the attacks.

During his first year in the Outpatient Department several attacks were stopped by carotid sinus pressure, but this method often failed. The frequency and severity of attacks gradually increased until they came on at least every 3 or 4 days, and lasted from 10 hours to 4 days. He became almost completely incapacitated.

In May, 1932, he began to receive injections of acetyl-β-methylcholin for attacks which could not be stopped by other means. Large doses proved necessary. Table 2 shows the date and amount of the injections.

During the fall and winter of 1932–1933 the attacks became more frequent and more prolonged. It became impossible to stop them by carotid or ocular pressure alone. Indeed, they stopped spontaneously very infrequently. But acetyl-β-methylcholin, in doses of 50 mg., continued to be effective, sometimes by itself, more often in combination with carotid pressure.

TABLE 2.—ACETYL-β-METHYLCHOLIN GIVEN TO T. H., 1932–1934.

1932:		1933:		1933:	
May 19	10 mg.	Jan. 4	50 mg.	June 14	50 mg.
	20 "	7	50 "		50 "
	30 "	17	50 "	24	50 "
	40 "	Feb. 7	50 "	July 14	50 "
26	40 "	Mar. 4	30 "	Aug. 7	50 "
July 15	50 "		50 "	8	50 "
Oct. 11	50 "	13	50 "		50 "
15	50 "	14	40 "	10	50 "
18	50 "	22	50 "	1934:	
27	50 "	April 28	40 "	Feb. 12	50 "
Nov. 17	50 "	May 15	30 "		
21	50 "		50 "		
25	50 "	June 9	50 "	*Total:*	
Dec. 1	50 "		50 "	40 injections,	
17	50 "			1.83 gm.	
30	50 "				
	50 "				

At the height of these symptoms he went into auricular flutter and remained in this rhythm for about 2 weeks. This led to admission to the ward, where tonsillectomy and dental extractions were performed. During the flutter, acetyl-β-methylcholin caused transient slowing of the ventricular rate but never changed the rhythm. He has had one brief attack of flutter since that time.

After spontaneous recovery from flutter he again had frequent attacks of paroxysmal tachycardia and appeared for an injection whenever he had a bad one. Though a second injection was occasionally necessary we were invariably able to stop the attacks. Carotid pressure alone gradually became more effective and the injections less necessary.

During the summer of 1933 he regained the power to stop some of the attacks himself, a thing he had been unable to accomplish for well over a year. Since February, 1934, he has not needed assistance. At present his attacks occur infrequently, and he soon brings them to an end by taking a deep breath and bending over. His heart area, which increased to +71% above predicted normal at the height of his symptoms, has now diminished to +27%. His general health is excellent, but it has seemed wise to limit his exertion somewhat. He is not working, being unable to find suitable employment. He is taking 0.3 gm. quinidin and 30 mg. of digitalis 3 times a day at present.

Discussion. *Toxic Effects and Their Relation to Syncope.* No evidence has appeared that acetyl-β-methylcholin is dangerous when administered in a proper manner and dosage. The fatal dose has not been reached; doses of 10 times the therapeutic have led to reactions, alarming but transient. Repeated doses have been administered without the development of any signs of chronic toxicity.

There is a striking similarity between the symptoms produced by an overdose of acetyl-β-methylcholin and the ordinary syncopal

attack. No case of the former has been observed with sufficient care to ascertain the order of development of the symptoms in those cases in which cardiac arrest and unconsciousness supervened; the state of mind of the attending physicians was not conducive to careful observation at that moment. But from a knowledge of the effects of smaller doses the picture can be put together. Objective symptoms common to the action of this drug and to syncope are fall in blood pressure, hyperpnea, sweating, salivation, nausea (occasionally vomiting), increase in pulse rate and, later, pronounced diminution of pulse rate.[6] In both there is prompt recovery without after effects. Atropin immediately relieves both.[5] All of the usual symptoms which follow an injection of acetyl-β-methylcholin have been described in certain cases of syncope. This is a striking analogy.

Certain obvious discrepancies may be explained by differences in position. After acetyl-β-methylcholin, given with the subject horizontal, the face always flushes; in syncope, the patient being in the upright position before collapse, flushing is sometimes seen, but pallor is more usual. In a general vasodilatation with the head raised the blood would be expected to drain into the dependent vessels, leaving those of the face empty; when the head is down, the vessels of the face would remain full. Flushing of the face was seen by Cotton and Lewis,[5] when, after syncope, the subject lay on the floor, and in other patients whose mild attacks did not progress to loss of consciousness.

Page[3] has pointed out the resemblance of the action of acetyl-β-methylcholin to that which follows the injection of pituitrin and pilocarpin into the lateral ventricles. He has also called attention to attacks occurring spontaneously in certain cases of hypertension, which resemble the action of acetyl-β-methylcholin in many of their features.[18] But in these cases the blood pressure rose, a feature I have seen very infrequently after acetyl-β-methylcholin, and much more often after acetylcholin.

It would be of great interest to test the blood of patients exhibiting such symptoms for derivatives of cholin. But, as the animal preparations necessary must be set up in advance, the test will be difficult to attain until a subject is found who will faint, or have an attack, on demand.

Relationship to Other Drugs Commonly Used in Cardiac Cases. Digitalis and quinidin are so often administered to patients with types of arrhythmia treated with acetyl-β-methylcholin that the question of the effect of the former drugs on the cardiac action of the latter frequently arises. The few preliminary pharmacologic experiments[4] have indicated that the cardiac action of acetyl-β-methylcholin may be altered by the other drugs. In my experiments on anesthetized cats and on isolated cat and rabbit hearts, quinidin has regularly diminished the cardiac action of acetyl-β-

methylcholin. But the diminution of the cardiac effect of acetyl-β-methylcholin after quinidin is not to be compared with the complete annulment of all action which follows atropin. Large doses will break through the quinidin effect both in the experimental animal and in the clinic.

The relationship between the actions of acetyl-β-methylcholin and of the digitalis group is more complicated. Pines has demonstrated that the cardiac action of acetylcholin is increased by strophanthin in certain animal experiments.[23] I have obtained a similar result with acetyl-β-methylcholin in isolated rabbits' hearts, and there is a little clinical evidence pointing in the same direction. However, in anesthetized cats and in isolated cat hearts I have not been able to demonstrate this reinforcing effect with any regularity. Also when strophanthin action has progressed to the point of block, or of alterations in the rhythm, doses of acetyl-β-methylcholin, previously effective, may have no effect whatever on the heart's rate. Therefore, my animal experiments have not yet yielded results consistent enough to afford a basis for predicting the effect of digitalis on the clinical action of acetyl-β-methylcholin.

In any event, those using acetyl-β-methylcholin in the clinic must be on the lookout for alterations in its effectiveness on the heart when their patients have been receiving quinidin or digitalis.

Concerning the Use of the Cardiac Action in Therapeutics. As the vagus-like effects of acetyl-β-methylcholin on the heart cannot be secured without a vigorous exhibition of the other actions of the drug, to attain maximum therapeutic results, with a minimum of discomfort to the patient, requires skill on the part of the attending physician. He must not only choose the dose and inject the drug, but he must then control the intensity of the effects. The degree to which the action, after subcutaneous injection, remains under control is surprising. By vigorous massage of the site of the injection it can be intensified; by applying a tourniquet above this site it can be diminished and, at any time, it can be brought to an end immediately by an injection of atropin.

In paroxysmal tachycardia, of the auricular or supraventricular types, an operator skilled in the control of the action and in pressure on the carotid sinuses should bring the attacks to an end immediately in about 90% of instances. The physician who, after the injection, stands idly by, may expect success in a much smaller per cent of cases.

In auricular flutter the drug is only occasionally successful in changing the rhythm. The infrequency with which such patients appear at the clinic and the seriousness of their condition in most instances have hindered the development of a technique which has much promise of success. The transient increase in block, regularly secured, is of no therapeutic importance, but an electrocardiogram taken during it may permit the identification of flutter in some instances hard to distinguish from paroxysmal tachycardia.

Little need be said regarding the advisability of using this very active and, to the patient, disagreeable remedy to stop attacks of paroxysmal tachycardia. The decision must rest on the condition of the individual patient. If the attack can be stopped by a simple mechanical method, as carotid sinus pressure, ocular pressure, etc., such means are to be preferred, although they may produce considerable discomfort in themselves. Patients whose attacks cause them little inconvenience may prefer to be let alone. On the other hand, those who suffer acute distress during attacks usually prefer to have them brought to an end at the cost of temporary discomfort. When experience has taught patients what to expect they find the action of acetyl-β-methylcholin less disagreeable than at the first trial, when the unexpected vigor of the action may frighten them. Several have come for treatment whenever they have had an attack which cannot be stopped by simple means. The rapid transition from the acute discomfort of tachycardia to the well-being which follows the resumption of normal rhythm is one of the striking clinical phenomena.

Summary. Acetyl-β-methylcholin has been used in the treatment of 75 attacks of paroxysmal tachycardia in 37 patients. In 66 instances (88%) the attack was promptly brought to an end.

The dosage necessary to terminate attacks of paroxysmal tachycardia varies with the age as well as with the weight of the patient.

Quinidin antagonizes the cardiac action of acetyl-β-methylcholin and may well be responsible for the failure to bring attacks of paroxysmal tachycardia to an end in certain cases.

In auricular flutter change in the rhythm can occasionally be brought about by acetyl-β-methylcholin.

In 1 case the frequency of ventricular extrasystoles was diminished by the drug.

The effects of overdosage of the drug are described. The symptoms are closely analogous to those of the ordinary attack of syncope.

REFERENCES.

1. Starr, I., Jr., Elsom, K. A., and Reisinger, J. A.: Acetyl-β-Methylcholin: I. The Action on Normal Persons, With a Note on the Action of the Ethyl Ether of β-Methylcholin, Am. J. Med. Sci., **186**, 313, 1933.

2. Starr, I., Jr.: Acetyl-β-Methylcholin: III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, With a Discussion of Its Action in Other Conditions, Ibid., p. 330.

3. Page, I. H.: Acetyl-β-Methylcholin (Mecholin): Observations Concerning Its Action on the Blood Pressure, Skin Temperature and the Heart, as Exhibited by the Electrocardiogram of Hypertensive Patients, Ibid., **189**, 55, 1935.

4. Starr, I., Jr.: A Note on the Antagonism Between the Cardiac Actions of Acetyl-β-Methylcholin and Acetylcholin, and That of Quinidin. To be published.

5. Cotton, T. F., and Lewis, T.: Observations Upon Fainting Attacks Due to Inhibitory Cardiac Impulses, Heart, **7**, 23, 1918–1920.

6. Starr, I., Jr., and Collins, L. H.: Physiological Studies of Faintness and Syncope, J. Clin. Invest., **9**, 561, 1931.

7. Hurtado, A., and Kaltreider, N. L.: Studies of Total Pulmonary Capacity and Its Subdivisions: Observations During Acute Respiratory Distress of Bronchial Asthma and Following Administration of Epinephrine, Ibid., **13**, 1053, 1934.

8. Comroe, J. H., and Starr, I., Jr.: Further Studies on the Pharmacology of Acetyl-β-Methylcholine and the Ethyl Ether of β-Methylcholine, J. Pharm. and Exp. Therap., **49**, 283, 1933.

9. Villaret, M., Vallery-Radot, Pasteur, Justin-Besançon, L., and Claude, F.: Recherches préliminaires sur les crises provoquées chez les asthmatiques par certains esters de la choline, Compt. rend. Soc. de biol., **116**, 1343, 1934.

10. Hunt, R.: Some Physiological Actions of the Homocholins and of Some of Their Derivatives, J. Pharm. and Exp. Therap., **6**, 477, 1914–1915.

11. Villaret, M.: Recherches physiologiques sur les dérivés de la choline, Compt. rend. Soc. de biol., **103**, 583, 1930; see also Ref. 15.

12. Simonart, A.: On the Action of Certain Derivatives of Choline, J. Pharm. and Exp. Therap., **46**, 157, 1932.

13. Hunt, R., and Renshaw, R. R.: Further Studies on Methylcholines and Analogous Compounds, Ibid., **51**, 237, 1934.

14. Villaret, M., Justin-Besançon, L., Cachera, R., and Said: Recherches préliminaires concernant l'action de la méthylacétylcholine chez les subjects normaux, Ann. de méd., **32**, 385, 1932.

15. Villaret, M., Justin-Besançon, L., and Cachera, R.: Recherches expérimentales sur quelques esters de la choline, Paris, Masson & Cie, 1934.

16. Simonart, A.: On the True Methylcholines, J. Pharm. and Exp. Therap., **54**, 105, 1935.

17. Major, R. T., and Cline, J. K.: Beta-methylcholine Chloride and Its Acetyl Ester, Ibid., p. 131.

18. Page, J. H.: A Syndrome Simulating Diencephalic Stimulation Occurring in Patients With Essential Hypertension, Am. J. Med. Sci., **190**, 9, 1935.

19. Alles, G. A.: Physiological Significance of Choline Derivatives, Physiol. Rev., **14**, 276, 1934.

20. Hunt, R.: Note on Acetyl-β-Methylcholine, J. Pharm. and Exp. Therap., **52**, 61, 1934.

21. Villaret, M., Justin-Besançon, L., Schiff-Wertheimer, and Gallois, M.: Les esters de la choline en ophthalmologie, Arch. d'ophtal., **49**, 129, 1932.

22. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-β-Methylcholine Chloride, J. Am. Med. Assn., **105**, 254, 1935.

23. Pines, I.: L'action de l'acetyl choline et du vague sur le cœur après administration de quelques poisons agissant sur le vague cardiaque, Arch. internat. de pharmacodyn. et de thérap., **49**, 91, 1934.

LUNG PUNCTURE IN LOBAR PNEUMONIA.

By S. W. Sappington, M.D.,
PATHOLOGIST, HAHNEMANN HOSPITAL,
AND
Grant O. Favorite, M.D.,
ASSISTANT PATHOLOGIST, HAHNEMANN HOSPITAL, PHILADELPHIA, PA.

(From the Clinical Laboratory.)

If lung puncture is to be practised as a diagnostic aid, especially routinely, it should be shown that it is a simple, safe method furnishing useful information. It is the purpose of this report to indicate that the procedure meets these requirements.

Lung puncture was first done by Leyden[1] in 1883. Since then, there are reports or mention of the method by Talamon,[2] Patella,[3] Tchistovitch,[4] Horder,[5] Eyre,[6] Rosenow,[7] Lister,[8] Clough,[9] Abra-

hams, Hallows, Eyre and French,[10] Netter,[11] French,[12] Nuzum, Pilot, Stangl and Bonar,[13] Thomas and Parker,[14] Armstrong,[15] Lyon,[16] Glynn and Digby,[17] Cecil, Baldwin and Larsen,[18] Stewart,[19] Alston and Stewart,[20] Cruickshank,[21] Shibley and Rogers.[22] In a number of these, the matter of lung puncture is only incidental or of minor mention in a paper devoted to another subject. In some instances[2,6,18,22] the punctures were done largely or exclusively postmortem. Lyon's[16] punctures were done entirely on infants and children: 20 of these were lobar pneumonias and 18 bronchopneumonias. Lung puncture studies were also done on influenzal pneumonias. Netter,[11] in the 1918 epidemic, recovered the influenza bacillus in 4 out of 8 lung punctures. Nuzum, Pilot, Stangl and Bonar,[13] in the same influenzal epidemic, did 36 lung punctures but failed to find the influenza bacillus, though the pneumococcus was recovered 11 times.

Most of the lung punctures were done on lobar pneumonias. Smears made directly from the products of lung suction afforded little information of value. Studies were more profitably directed toward the percentage of positive cultures from puncture as well as the number of cases in which the pneumococcus was isolated in purity. Then followed studies on the types in lung puncture cultures and comparison of these results with the sputum findings. Attention was also paid to the stage of the pneumonia in which the pneumococci were recovered and the relation to the crisis, prognosis and virulence. Patella[3] did punctures before and after the crisis finding large numbers of pneumococci before crisis and obtaining inconstant results after crisis. Rosenow[7] noted that while positive cultures were obtained all through the course, the percentage of positive results were much higher in the early stages in favorable cases and tended to diminish in these cases as crisis was approached. On the other hand he found that positive cultures persisted to death in unfavorable cases. Thomas and Parker,[14] in general, confirmed Rosenow's work and showed that where puncture cultures were positive after the sixth day, the mortality was 56% compared with 23.5% in those with positive results up to the sixth day only. They found some cases, however, with positive cultures after the crisis and elaborated a theory of antibacterial and detoxifying mechanisms working independently. The matter of pneumococcic virulence as indicated by the presence of smooth or rough forms and the degradation of S to R forms and their relation to recovery was studied by Shibley and Rogers[22] by lung puncture with somewhat suggestive results, though it would appear that further studies on more cases were necessary for definite conclusions.

The percentage of positive lung puncture cultures in lobar pneumonia during life is, according to various observers, around 50%. Lister[8] in 200 cases got 50% of positives; Thomas and Parker,[14] 59% in 73 cases; Glynn and Digby,[17] 37.5% in 44 cases; Stewart,[19]

76% in 17 cases; Cruickshank,[21] 50%; and Bullowa,[23] about 35% of positives in 1467 cases. The results probably depend on the culture technique as well as the stage and the case of pneumonia. Mostly, pneumococci were found in pure culture, though at times other organisms were also recovered or later contaminated the cultures. The prognostic value of lung puncture has already been indicated in the observations of Rosenow,[7] Thomas and Parker,[14] and Shibley and Rogers.[22] To this may be added the information furnished by typing. In previous studies on lung puncture the typing was confined to the 4 types then recognized. With the 32 or more types now known, and with the utilization of the Neufeld method of typing, the usefulness of lung puncture has, we believe, been extended. It is with this phase that this paper deals.

Lung puncture has never become a popular method of diagnostic approach to pneumonia. The reason for this is almost certainly a hesitancy over a real or apparent danger in the procedure as well as a lack of demonstration of its practical usefulness. Horder[5] as long ago as 1909 published a paper entitled "Lung Puncture: A New Application of Clinical Pathology," a heading which hints at a useful method. Among those who have had considerable experience with lung puncture[12,14,16,17,19] there is general agreement that the danger is negligible. Glynn and Digby[17] in reviewing the subject conclude that "the examination of lung juice in pneumonia is a valuable but neglected aid to exact bacteriologic diagnosis, especially in children. If properly performed, the danger is negligible, except that hemorrhage may occasionally occur." Bullowa,[23] who has had extensive experience with lung puncture, or as he prefers to call it, lung suction, uses the method routinely in a very large pneumonia service at the Harlem Hospital and also finds the danger of no moment in properly selected early cases of lobar pneumonia, employing his technique. He had no increase in empyema, rarely a slight or unimportant hemorrhage and occasionally a pneumothorax. There is unanimity of opinion among observers that there is no increase in the incidence of empyema after lung puncture. Slight transient hemorrhage after puncture is mentioned by a number of writers. Pneumothorax is a rare but real sequel but the present view of its therapeutic value would make it an advantage rather than a disadvantage to the patient. Sudden death is mentioned only once in the references here listed,[14] and must be excessively rare from lung puncture. Collapse or sudden death, following thoracentesis for pleural effusion or lung conditions is said[24] to be due in nearly all cases to air embolism, the point of an unattached, usually large, needle or trocar entering a vein and permitting air suction during inspiration. With the needle firmly attached to a syringe this danger should be eliminated. It is assumed that one's knowledge of anatomy and physical diagnosis will exclude any such unnecessary accidents as puncture of the heart or large vessels or an aneurysm.

Finally improvements in technique, such as the use of a small needle and restriction of any movement of the needle when in the lung, should reduce sequelæ to a minimum.

Technique. In general, after preliminary cleansing of the skin and anesthetization of the underlying tissues with 0.5% procain solution, the consolidated lung is punctured with a long needle attached to a syringe which may or may not contain broth or saline. Strong suction is made, and the resulting withdrawn material distributed to culture media. The skin is usually cleansed with iodin and alcohol. In most cases, local anesthesia is recommended. We did not find it necessary. The needles formerly used were large size and Thomas and Parker[14] employed a 16 gauge. Most operators now advise an 18 to 20 gauge needle. Bullowa[23] uses a very fine, flexible, stainless steel needle, 10 cm. in length, 22 gauge, medium point and 35 degree bevel. The length generally suggested is 10 cm. The syringes advised are of 10 to 20 cc. size. Some use suction as the needle is withdrawn from the lung while others[23] employ suction both as the needle enters and leaves the lung. Thomas and Parker[14] and Stewart[19] use a dry syringe. Glynn and Digby[17] draw 0.5 cc. of saline in the syringe, and after the needle is introduced inject this fluid into the lung and then make steady suction. Bullowa[23] has 3 to 4 cc. of blood broth in the 20 cc. syringe at the time the puncture is made so that the withdrawn material mixes at once with this culture medium. The medium also assists in expelling what remains in the needle. At times, Bullowa[23] finds, some of the contents of the needle may be expelled on a slide for direct typing. Those who use a dry syringe usually rinse out the withdrawn matter with plain, phosphate or glucose broth. The withdrawn lung juice or blood, mixed or unmixed with broth is distributed to culture media such as serum or blood agar plates, blood or chocolate agar slants and broth. Sometimes,[19] a mouse is injected with the broth washings.

The technique we employed was as follows: The location of the consolidated area was carefully located by physical signs and Roentgen ray. Puncture was not done unless there was definite evidence of pneumonia. Over this area of maximum signs and shadow, the puncture was made. This usually was over the posterior inferior aspect of the chest, but we frequently entered the lung without damage through the upper chest posteriorly or anteriorly (infraclavicular region) or in the axilla. The skin over the prospective site was thoroughly swabbed with alcohol only. No anesthetic was used and patients made little or no complaint. A dry 5 cc. glass syringe with a 6 cm. No. 20 needle was employed. The needle was entered 5 or 6 cm. and strong suction made on withdrawal. The needle, after introduction, was not moved about or changed from its primary position in the lung except to withdraw it. If negative pressure was encountered on suction the results were usually good: if positive pressure was found and the piston of the syringe slipped back easily, the results were usually disappointing. Commonly a little bloody matter was obtained. This might be only a drop or two or as much as 1 cc. Not infrequently nothing grossly visible was removed or a mere serous moisture. Occasionally just before complete withdrawal a little clear fluid entered the syringe, evidently a thin pleural exudate. In this instance, positive cultures were not always obtained. After the needle was removed from the lung, the contents of the syringe were at once washed into a single tube of slant agar at the bottom of which were 1.5 cc. of plain broth pH 7. This was done by entering the small 5 cc. syringe and needle into the agar tube so that the needle reached to the bottom of the tube. The broth was then sucked up into the syringe and expelled, and this was repeated 4 or 5 times. Even when there was no visible withdrawn matter the procedure was

followed and positive cultures were not infrequently obtained. Especially was this prospect good if a few fibrin flakes were seen. The tube was at once incubated and examined at short intervals later, say 2, 4, 6 and 12 hours, by making spreads of the broth at the bottom of the slant and the agar surface just above it.

The first evidence of growth, if the examination of the broth was made only a few hours after the puncture, was at times only a few pneumococci. At other times, the first examination showed numerous organisms. After their first appearance, even in very small numbers, the pneumococci increased very rapidly. As soon as they were in sufficient numbers for typing, this was done by the Neufeld method, using a small drop of broth against one or two of serum. A culture was considered ripe for typing when there were at least 10 bacteria per oil-immersion field. Fewer bacteria, when diluted with typing serum and methylene blue, required too tedious a search to find the organisms. Pneumococci cultured this way showed beautiful capsulation under the action of the serum in primary cultures as young as 2 hours or as old as 36 hours. The secondary growths did not show it. When the primary growth was injected into a mouse, the peritoneal wash also showed excellent capsulation with serum.

Findings. Sixty cases of lobar pneumonia were studied, 57 pneumococcic and 3 streptococcic. Of these, 54 (90%) yielded positive lung puncture cultures suitable for direct typing of the pneumococci by the Neufeld method and for cultural and morphologic recognition of the type streptococcus. It required 68 punctures in the 60 cases to obtain the aforementioned figures. Of the 60 initial or primary punctures, 49 (81.6%) gave positive cultures. Seven patients were punctured a second time, 4 yielding positive cultures; 3 punctures were done on only 1 patient, the third being positive. From the point of view of the number of punctures, 54 out of 68 (79.4%) were positive.

The lung puncture cultures were actually or practically pure in every instance. In 54 cultures only a single organism grew and this bacterium was unquestionably the causative factor in the infection. In 3 instances, after 48 hours, a contaminating white staphylococcus was also found but this was after the diagnostic work had been done and the subcultures made. In the first 48 hours all cultures were pure. A pneumococcus was recovered in 51 cases; a hemolytic streptococcus in 3. The pneumococci fell into the following types: Type 1, 12 cases; Type 2, 15 cases; Type 3, 3 cases; Type 4, 2 cases; and 1 case each of Types 5, 7, 8, 9, 14 and 18; 13 remained unclassified, lacking appropriate typing sera. The streptococcus cultures were easily identified by the marked hemolysis on the primary blood agar tube, making subcultures for further study unnecessary.

There would be no justification for doing lung puncture in lobar pneumonia with a view to serum therapy unless the organism could be recovered and typed within a short time. We endeavored to study this phase of the problem by examining the broth repeatedly at short intervals, though this was not always practical when the puncture and culture were made late in the day. In 33 of the positive punctures, the cultures were examined at 1 or 2-hour intervals

and the organisms found within 8 hours. At the end of 3 hours, 10 cultures were positive while at the end of 6 hours, the number increased to 29. Twenty-one punctures and cultures were made late in the afternoon and not examined until the next morning. The earliest positive culture fit for typing was in 2 hours; the latest, 36 hours. Thus, over half of the puncture cultures were positive within 6 hours and these figures almost surely would have been higher had frequent examinations in all cases been done. After the initial lag phase, the number of bacteria increased rapidly within a very short time. The first finding might show only 5 or 6 organisms in the whole spread examined rapidly; while an hour later, the same culture would show organisms in every oil-immersion field. Plotting the total number of positive cases for the time interval, the resulting curve (Chart I) simulates the accepted growth curve of bacteria.

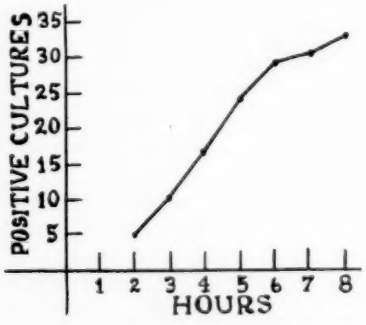

CHART I.—The number of cultures positive at the various hours after puncture.

The distribution of punctures with respect to the course or the day of the disease was fairly uniform. In the first 4 days of the disease 34 were done, 21 of these in the first 2 days; 29 from the fifth to the tenth day inclusive. In 5 cases, the day of the disease could not be fixed definitely. With the exception of the third day, when a comparatively small number of punctures were done, the percentage of positive cultures was consistently high during the first 6 days of the disease (Chart II). It may be noted that 10 punctures were made from the seventh to the tenth day inclusive. Of these, 7 were positive with 5 deaths; 3 were sterile with no deaths.

Sputum was present at some period of the disease in 57 cases. Of these, the sputum was present and typed at the time the lung puncture was done in 35 cases. It was satisfactory for direct Neufeld typing in 32 instances and by the mouse method in 3 instances. In 22 cases, the sputum was either absent or not obtainable up to the time the puncture was made. In 9 of these the sputum was later obtained and typed. A few cases had no sputum at any time. In 44 cases in which typing was attempted, the exact type was

determined in 25. In the remainder, typing was unsuccessful for want of appropriate antiserums. In the 25 classified sputa, the type ascertained was the same as that found in the corresponding lung puncture culture. In 24 the agreement was determined on the first typing. In 1 case only, a Type 4 was not found on the first attempt as was expected from the Type 4 lung culture: on the second attempt, however, Type 4 was demonstrated in the sputum.

The 3 streptococcus pneumonias were lobar in distribution and hemolytic in type and lung punctures were positive in all cases. The hemolytic type made recognition easy.

Blood cultures were done in 17 cases, 5 of which proved positive, 1 of these being a streptococcus hemolyticus, the others pneumo-

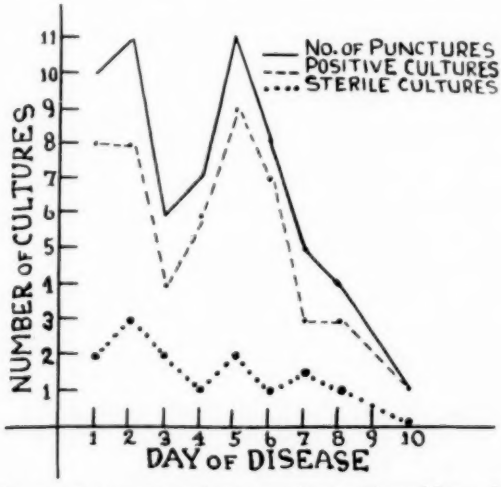

Chart II.—The correlation of 63 lung punctures, 49 positive cultures, and 14 sterile cultures with the day of disease.

coccic. In the 4 pneumococcic positives the blood and lung types agreed.

The mortality for the entire series was 40%, 2 of the 3 streptococcus pneumonias dying. Autopsies were held in 10 cases, enabling us to examine the site of lung puncture. No trauma was demonstrated from the puncture and in most cases it was difficult or impossible to find the puncture site. In 1 case in which there had been some hemorrhage after puncture no blood was found in the lung or bronchi and there were no signs of injury.

Sequelæ. In the natural course of lobar pneumonia, empyema is regarded as the most important frequent complication and one that might theoretically be anticipated after lung puncture. The frequency of this complication varies, depending in part upon the type of the organism. In Cecil's[25] large series of pneumococcus

pneumonias, the incidence of empyema ranged from 3.5 to 6.8% in the various types and averaged 5.1% for all types in 1913 cases. In our series of 57 pneumococcus pneumonias, empyema occurred in 5.3% of cases. But if the incidence of empyema be based on the number of lung punctures, which would seem logical, the incidence in the pneumococcus pneumonias was but 4.6%. The types found in the pneumococcus cases were 1, 3 and 8, and these agreed with the lung puncture types. One of the 3 streptococcus pneumonias developed empyema.

Hemorrhage developed immediately following lung puncture in 3 cases. In 2 it was trivial and only consisted of little bloody sputum for a few hours after the puncture. In another case, the bloody expectoration continued for some days, though it was never large in amount. This patient died of very extensive multilobar pneumonia and autopsy, as cited, showed no trauma or collected visceral blood.

Pneumothorax developed in 1 case. This occurred in the early part of our investigation, the patient being punctured 3 times at one sitting and the needle moved about after entering. We attribute this accident to our own poor technique at that time, though undoubtedly pneumothorax occurs occasionally when the technique is not to be criticized. This patient was actually improved after this pneumothorax.

There were no cases of sudden death after puncture or death attributable in any way to the procedure.

Comment. This review and study indicate, we believe, that lung puncture is reasonably safe and useful. Out of about 2000 lung punctures collected, there was only 1 case of sudden death[14] and, as a matter of fact, in this case the chest was being tapped for suspected fluid and the lung punctured unintentionally. There is no instance in this large series, of death from hemorrhage or pneumothorax. It is true, of course, that sudden death may follow chest puncture and Russell,[26] in criticizing Horder's paper[5] on lung puncture in 1909 cited 11 deaths following chest tap. Horder[27] effectively replies to this and concludes that this contingency is the rarest of events. And in the last 25 years, and particularly lately, with improved technique and diagnostic skill, the danger of sudden death or serious hemorrhage seems to have almost disappeared so that the conclusion of many writers that the danger is "negligible" would appear justified. In furtherance of this we would urge strict adherence to the technique cited, especially the use of small needles.

The usefulness of the procedure is seen in fact that 90% of 60 puncture cases yielded positive cultures which were pure and immediately adapted to Neufeld typing in the case of pneumococci. Half of the positive cultures were positive within 6 hours thus permitting early typing and therapy. We were able to type 38 of the positive

lung cultures as against 25 of the sputum organisms. Had all of the 32 pneumococcic antisera been available, these figures would of course have been increased for both. The advantage of lung culture typing is seen in the fact that in 22 of our cases the sputum was absent or not obtainable up to the time the puncture was made. Prognostic data in our small series were insufficient but what there are agree with those of Rosenow[7], and Thomas and Parker[14] in indicating that the viable lung organisms disappear in the later days in favorable cases and persists to death in unfavorable ones.

The 100% type agreement of the organisms of the sputum with those of the lung puncture cultures shows the reliability of the sputum in this respect. Therefore, in cases where the sputum is available and typable, lung puncture is unnecessary.

The technique herein detailed, the use of a single tube of blood agar with 1.5 cc. of plain broth at the bottom of the tube, is so simple and adequate that it is to be recommended. The very rapid growth of the lung organisms in this small amount of broth plus the few drops of lung blood or exudate allows early typing of the pneumococcus and usually the recognition of the type streptococcus.

Four of the lung punctures were done after antipneumococcus serum had been administered: all 4 of these gave positive cultures. Two Type 1 cases gave positive cultures 3 and 24 hours respectively after 20,000 units of serum. A Type 2 case was positive 3 hours after 10,000 units of serum: and another Type 2 case gave a positive culture 24 hours after 20,000 units. Three recovered; 1 Type 2 case died.

One patient gave a Type 2 pneumococcus in the sputum and from the lung. Reference to a hospital admission 8 months previous, showed he then had Type 2 pneumonia. He recovered.

Summary. With a simple and apparently safe technique, 60 cases of lobar pneumonia (57 pneumococcic and 3 streptococcic), were subjected to diagnostic lung puncture. Positive cultures, suitable for typing, were obtained in 90%, half of these within 6 hours. Lung puncture cultures made 3 and 24 hours after the administration of antipneumococcus serum were positive. In 25 cases in which both the lung and sputum pneumococcus were typed, there was 100% agreement. Where sputum is at once available, therefore, lung puncture is unnecessary. In 22 of the cases, however, the sputum was either absent or unobtainable at the time the lung puncture was made. The method is, therefore, recommended for early diagnosis and typing when sputum is not as quickly available.

REFERENCES.

1. Leyden, I.: Deutsch. med. Wchnschr., **9**, 52, 1883.
2. Talamon, M. LeD.: Bull. soc. anat. de Par., **63**, 475, 1883.
3. Patella, V.: Atti d. R. Academia di Roma, **4**, 1888.
4. Tchistovitch, N.: Ann. de l'Inst. Pasteur, **18**, 304, 1904.

5. Horder, T. J.: Lancet, **2**, 1345, 1909.
6. Eyre, J.: J. Path. and Bact., **14**, 160, 1910.
7. Rosenow, E. C.: J. Infect. Dis., **8**, 500, 1911.
8. Lister, F. S.: An Experimental Study of Prophylactic Inoculation Against Pneumococcal Infection in Rabbit and Man, Publ. So. African Inst. Med. Res. Johannesburg, No. 8, October 1, 1916.
9. Clough, M. C.: Johns Hopkins Hosp. Bull., **28**, 306, 1917.
10. Abrahams, A., Hallows, N. F., Eyre, J. W. H., and French, H.: Lancet, **2**, 377, 1917.
11. Netter, A.: Bull. Acad. de Med., **80**, 275, 1918.
12. French, H., quoted by Glynn, E. E., and Digby, L.: Ref. 17.
13. Nuzum, J. W., Pilot, I., Stangl, F. H., and Bonar, B. E.: J. Am. Med. Assn., **71**, 1562, 1918.
14. Thomas, H. M., and Parker, F.: Arch. Int. Med., **26**, 125, 1920.
15. Armstrong, R. R.: Brit. Med. J., **1**, 259, 1921.
16. Lyon, A. B.: Am. J. Dis. Child., **23**, 72, 1922.
17. Glynn, E. E., and Digby, L.: Bacteriologic and Clinical Observations on Pneumonia and Empyemata, with Special Reference to the Pneumococcus and to Serum Treatment, Great Britain Nat. Health Ins. Med. Res. Com., Special Report. Series 79, p. 105, 1923.
18. Cecil, R. L., Baldwin, H. S., and Larsen, S. P.: Arch. Int. Med., **40**, 253, 1927.
19. Stewart, D.: Lancet, **2**, 520, 1930.
20. Alston, J. M., and Stewart, D.: Brit. Med. J., **2**, 860, 1930.
21. Cruickshank, R.: Glasgow Med. J., **115**, 59, 1931.
22. Shibley, G. S., and Rogers, E. S.: Proc. Soc. Exp. Biol. and Med., **30**. 6, 1932–1933.
23. Bullowa, J. G. M.: Personal Communication.
24. Medical Science: Abstracts and Reviews, **3**, 521, 1921.
25. Cecil, R. L.: Text-book of Medicine, 3d edition, Philadelphia, W. B. Saunders Company, 1934, p. 30.
26. Russell, A. E.: Lancet, **2**, 1539, 1909.
27. Horder, T. J.: Correspondence, Ibid.

THE ASSOCIATION OF ERYTHREMIA AND DUODENAL ULCER.

By Manfred Kraemer, M.D.,

associate, gastroenterology, newark presbyterian hospital; assistant in medicine, newark city, st. james and beth israel hospitals,

and

Maurice Asher, M.D.,

formerly gastroenterologist and chief of medicine, newark beth israel hospital, newark, n. j.

In August, 1932, Morris[1] *et al.* inferred from their findings in the blood in erythremia that the disease was due to an overproduction of the blood-forming hormone, which they named "addisin." They propounded the theory that erythremia was due either to excessive secretion of "addisin" by the stomach or due to an increase in the susceptibility of the bone marrow to stimulation by "addisin." They suggested that erythremia be treated by lessening the gastric secretion. A year later the Morris group[2] definitely concluded that "addisin," the hemopoietic factor secreted in the normal stomach, was identical with the "intrinsic factor" of Castle.[3] They treated

a case of erythremia by lavaging the stomach 3 to 4 times weekly in an attempt to diminish the body's supply of "addisin." In the course of 6 months their patient's blood count fell from 10 to 5.3 millions. A few months after the lavage was discontinued the count had again risen to 10.2 millions.

Their patient had a duodenal ulcer associated with the erythremia. This association of erythremia and duodenal ulcer seems to be more than coincidental. The subject of the association of these two diseases has recently been discussed by Boyd,[4] who, after reviewing the literature and reporting a case, reached the conclusion that polycythemia bore a causal relationship to duodenal ulceration.

Wilbur and Ochsner[5] have also abstracted the literature regarding the concurrence of these diseases and have carefully investigated 143 case records of erythremia at the Mayo Clinic. In 8% of their cases there was roentgenologic evidence of gastric or duodenal ulceration. In a control series of 200 cases of hypertension the incidence of ulcer was only 2%.

We have recently observed 2 patients having erythremia and duodenal ulcer associated. Both patients were Russian Jews employed in tailoring establishments. The gastro-intestinal complaint was predominant in both cases. The first case presents nothing of unusual interest, and it is offered merely because it adds another case to those already reported of the association of these two diseases.

Case Reports. Case 1. S. B., a white male, aged 52, complained of pain at the ensiform cartilage after meals. The pain was relieved by food. This symptom had persisted for 2 years, and the patient had had no illness of significance previously. The skin of the face was purplish-red and the mucous membrane of the mouth was deep red. There was marked epigastric tenderness. The red blood cells numbered 9,400,000 and the hemoglobin was 140%. Roentgen rays taken elsewhere showed a duodenal ulcer. The patient refused to permit extensive study of his case as he was interested only in relief from the ulcer symptoms and could not be persuaded of the significance of his blood dyscrasia. He was given an alkalin powder and a hyperacidity diet and was not heard from again.

The second patient was more coöperative. We attempted a series of lavages, not only to relieve the ulcer symptoms but also in the hope that the erythremia might improve as it did in the case treated by Morris and his associates.

Case 2.—J. F., a white male, aged 49, came to us on November 21, 1933, for relief of "stomach trouble." He complained of epigastric pain and sour water brash. The symptoms appeared about 3 hours after meals and were relieved by food. These complaints had their onset in January, 1933. He sought medical advice in the summer of 1933, and was told that he had an "acid stomach" and was treated unsuccessfully with diet and alkalis by two successive physicians.

In addition to this gastro-intestinal history, he informed us that he was a sufferer from polycythemia vera. He had become aware of this blood dyscrasia early in 1932. At that time a sebaceous cyst was removed

from the back of his neck at a physician's office. The bleeding was so severe that to control it the patient was removed to a hospital. There the diagnosis of erythremia was made. From June, 1932, until February, 1933, he was treated for the erythremia at the Stuyvesant Square Hospital Clinic of New York. This clinic was kind enough to supply us with information about the patient. He had been given phenylhydrazin in capsules. The red cells fell from 9 to 6 million, but returned again to 9 million after the drug was withdrawn in February, 1933.

Physical examination: Blood pressure, 150/100. Skin of face and hands was of a purplish hue. Mucous membrane of the mouth and pharynx was deep red to purple in color. The heart, lungs, abdomen and reflexes showed no abnormalities. However, a Roentgen ray film of the chest showed considerable increase in bronchial and vessel markings.

Laboratory examination: The urine contained a large quantity of albumin and many granular casts. The red blood cells numbered 8,750,000; hemoglobin, 135%. Fractional gastric analysis showed a curve of hyperacidity, continuing high over most of the test period of 2 hours. Occult blood was present in all specimens. Gastro-intestinal fluoroscopy and Roentgen-ray films disclosed the typical deformity of duodenal ulcer.

Diagnosis: Duodenal ulcer. Erythremia. Chronic nephritis.

Course: Knowing that gastric lavage would greatly relieve the ulcer symptoms, and in view of the benefits obtained by Morris in erythremia, we employed this treatment in our case. We prescribed a bland diet and alkalis and instituted biweekly lavages, which were carried out over a period of 3 months. The patient arrived at the office for his lavage about an hour after a breakfast of a cup of coffee. The stomach was washed 10 times at each visit with 300-cc. portions of dilute bicarbonate of soda solution, administered and withdrawn through a narrow Rehfuss tube. After a few weeks, occult blood was absent from the return wash water, and after 2 months the symptoms of ulcer disappeared. The red blood counts taken from time to time were as follows:

November 21, 1933: 8,750,000; hemoglobin, 135%.
December 8: 9,000,000; hemoglobin, 138%.
January 9, 1934: 9,070,000; hemoglobin, 144%.
February 23: 9,500,000; hemoglobin, 130%.

When the patient was cured of his painful ulcer symptoms, and since he knew that his red blood cells were not being reduced, he was no longer content to continue the lavages. In March, 1934, treatment was discontinued. A follow-up in May, 1934, revealed that the patient was still free from his ulcer symptoms and was receiving Roentgen ray therapy for his erythremia.

Comment. Apparently not all cases of erythremia are benefited by lavaging "addisin" from the stomach. It is possible that we did not carry out frequent enough washings. Oerting and Briggs[6] lavaged their patients 4 to 6 times daily, and thus obtained a reduction in the red blood cells. The difficulty of persuading a symptom-free patient to consent to such a procedure can readily be realized. However, it is only by trying this treatment on all cases of erythremia that its values can be determined. Lavage of the stomach affords such great relief to ulcer sufferers that they are willing to continue the treatment for long periods of time.

Should a patient with erythremia and duodenal ulcer associated show a marked reduction in erythrocyte count after gastric lavage, gastrectomy might afford permanent cure of both afflictions. This

operation would remove the source of "addisin" and at the same time cure the ulcer. At least, it is interesting to speculate on curing erythremia by gastric resection.

REFERENCES.

1. Morris, R. S., Schiff, L., and Foulger, M.: Erythremia, a Theory Regarding Etiology, J. Med., **13**, 318, 1932.
2. Morris, R. S., Rich, M. L., Schiff, L., Foulger, J. H., and Felson, H.: Observations on Addisin in Diseases of the Blood, Ann. Int. Med., **6**, 1535, 1933.
3. Castle, W. B., Heath, C. W., and Strauss, N. B.: Observations on Etiologic Relationship of Achylia Gastrica and Pernicious Anemia, Am. J. Med. Sci., **182**, 741, 1931.
4. Boyd, W.: The Relationship of Polycythemia to Duodenal Ulcer, Ibid., **187**, 589, 1934.
5. Wilbur, D. L., and Ochsner, H. C.: The Association of Polycythemia Vera and Peptic Ulcer, Ann. Int. Med., **8**, 1667, 1935.
6. Oerting, H., and Briggs, J. F.: The Influence of Gastric Lavage on Familial and Non-familial Erythremia, J. Am. Med. Assn., **104**, 250, 1935.

AMEBIASIS AND CANCER OF COLON.

By Alfred C. Reed, M.D.,
Professor of Tropical Medicine, Hooper Foundation, University of California,
and
Hamilton H. Anderson, M.D.,
Assistant Clinical Professor of Pharmacology, University of California Medical School, San Francisco, Calif.

(From The Pacific Institute of Tropical Medicine within The Hooper Foundation of the University of California.)

In his *Clinical Medicine*, Trousseau[1] says, "I repeat that dysentery is the most formidable and dangerous of all epidemic diseases. Even when patients have resisted its first assaults, and seem to be reaching convalescence, danger is not past, and there are evil consequences to be dreaded after the disease." Trousseau's characterization included amebic dysentery and seems to have particular force when we consider so serious a sequel of it as cancer of the large bowel.

Attention has been called frequently to amebic lesions of the colon which were mistaken for carcinoma. Cancer has been mentioned by various writers as a possible sequel of amebic dysentery. Remarkably little has been reported on the association of cancer with amebic dysentery, and the masking of malignant symptoms by indications of amebiasis.

The first half of the picture, amebic lesions simulating cancer, has been presented, among others by Desjardins,[2] who states that undoubtedly operations are performed under this wrong diagnosis. He calls attention to masses consisting of a true neoplasm of amebic origin, or an inflammatory mass secondary to an amebic ulcer, or to

an amebic ulcer alone. He describes a characteristic patient, aged 40 to 50 years, with persistent attacks of pain in the right lower quadrant, difficulty in defecation, alternating constipation and diarrhea, with mucoid movements at times bloody. Examination shows a hard irregular mass either fixed or movable with the colon. The Roentgen ray may show a filiform narrowing. The whole picture seems one of cancer but the mass is made up of spastic bowel and inflammatory products of an ulcer.

Gunn and Howard[3] report 3 cases of amebic granulomas simulating cancer. The pathology in these cases consisted of persisting, "isolated, chronic ulcer with progressive erosion of the wall of the bowel." Edematous fibrous granulation tissue was produced in large quantity resulting in definite tumor masses. These amebic granulomas may "give symptoms, physical signs, and radiologic appearances that may be identical with those produced by carcinoma." This important report deserves careful study. The authors comment on the rarity of reported amebic tumor formation, and could find only 6 authentic cases beside their own. They note that amebas may appear in the stools only occasionally, if the amebic colonization is limited to the tumor mass, thus making preoperative diagnosis even more difficult. Rogers[4] refers to 2 cases of supposed cancer, in which amebas were found, and which were cleared up by emetin treatment. The present writers have seen 3 cases in which definite tumor masses were found in the colon but in none was the mass isolated, arising from a single ulcer as described by Gunn and Howard. Extension of the lesion to various parts of the colon is strongly against a diagnosis of cancer. Amebic tumors tend to disappear with medical treatment but their failure to do so does not rule out an amebic lesion. Gunn and Howard observed coexistence of amebiasis and cancer, and note that Roentgen ray findings may not distinguish between the two.

A case of polyposis of the colon has been described by Hines[5] in which "the colon mucosa presented no gross signs of ulceration, but was the site of multiple confluent polypoid masses." Hines describes the frequent formation of polypoid masses at the margins of healing dysenteric lesions. He quotes Kaufmann[6] who noted their presence in tuberculous ulcers of the colon, and refers to descriptions of their occurrence in amebic lesions. Here we have a possible method for the development of cancer from an amebic lesion, through the transitional stage of polyps or small adenomas.

Cancer of Colon and Rectum. Carcinoma of the colon is nearly always primary. Rarely it has been reported as secondary to a tumor higher in the intestine, when direct implantation and not metastasis is probably the explanation. Rarely, also, multiple growths in the colon have been reported. In the colon carcinoma metastasizes late and slowly to the liver and lymphatics, and tends to remain localized for a long time. Metastasis elsewhere is uncom-

mon, but may occur as shown in Case 3 below. Cases have been reported from early childhood to extreme old age. In general, rectal cancer tends to appear at a later age. In the colon, spread is by contiguity and by extension of an intrinsic tumor which thus tends to cause obstruction. Obstruction is rarely or never complete but commonly results in proximal dilatation and hypertrophy of the bowel and may cause intussusception or angulation. The rate of growth is characteristically slow. The favored site is in the sigmoid, and descending colon, followed by the ileocecal region and cecum, and then the hepatic and splenic flexures.

In the rectum, Tuttle[7] placed 67% at the rectosigmoid junction, 26.3% in the ampulla and 6.7% in the anus. Epithelioma can occur only at the anal skin edge and only an involvement of skin tissue can lead to extension to the inguinal glands. Rectal growths tend to spread in all directions with circular extension common. Rectal cancer is some 8 times more common than colonic cancer. The great majority of cancers of the colon and rectum are adenocarcinomas, which tend to metastasize less rapidly than other forms. Scirrhous carcinoma and lymphosarcoma are uncommon. Lymphosarcoma is amenable to Roentgen ray treatment and Roentgen ray examination after a 2 weeks' interval will show definite regression.

Clark,[8] in reviewing the distribution and complications of amebic lesions in 186 postmortem examinations performed by him, reports the following: "About 60% of the series possessed ulcers more or less all through the colon, while 40% had a local distribution in the more dependent parts of the colon and appendix. The local incidence for age and number of lesions can be placed in the following order of importance: the cecum and ascending colon, the rectum and sigmoid, and the appendix. The results are in conformity, more or less with the report of Kartulis except in regard to the appendix." Clark states elsewhere that but 27 of the 186 cases had a known history of one or more previous attacks of amebiasis and these patients were under treatment for the disease. This shows a striking similarity in the sites of election in amebiasis and in cancer of the large bowel.

Cancer is prone to follow simple tumors such as polyps and adenomas of the colon and to develop at points of long-continued irritation. Such points are afforded by long-standing ulcers, fistulas and constrictions. Chronic amebiasis affords an excellent background, therefore, and cancer must be considered as a possible sequel. The exciting cause of the change from chronic benign process to rapid malignant process is unknown and no method is available for diagnosing the imminence or the occurrence of this transition. Altered sedimentation rate and other blood changes are not helpful because of the close masking intermixture of secondary bacteria with the entire process, both in its benign and in its malignant phases. Also, the response to bacterial invasion overshadows the

body reaction to malignancy so far as the sedimentation rate is concerned. Cure of colonic and rectal cancer is exactly proportioned to earliness of diagnosis, permitting surgical removal in an operable stage, or Roentgen ray treatment in the case of lymphosarcoma. Obstructive symptoms usually, but not always, indicate inoperability (see Case 1 below). The patient's future thus depends on his early consultation with the physician, when any part of the symptom-picture noted below arises, and very definitely depends on consideration, by the consultant, of the possibility of cancer. Furthermore, when cancer can be proved absent, care must be exercised to remove accessible benign growths, to correct so far as possible mechanical defects and to cure as quickly as possible specific dysenteries and amebiasis. The advisability of colon resection as a preventive measure must be considered in cases of polyposis especially where the favored cancer areas are concerned.

The symptoms of cancer of the colon may be summarized as follows:

1. *Pain.* This may be merely a sense of discomfort and vague unrest with undue consciousness of the abdomen. Frank pain is extremely variable, may be absent until late, but, in our experience, is usually fairly early and decidedly significant. It tends to be localized although not necessarily in the region or zone of the lesion. It may be in the sacrum or anywhere in the abdomen. It may be of a burning character, intermittent or constant, or periodic. It may be associated with difficulty in securing free evacuation of the bowels. It may be due entirely to partial obstruction, which, in the descending colon and sigmoid, may disappear completely, not to recur even for several months. Obstructive pain may appear suddenly and acutely, with nausea and vomiting and the general picture of acute obstruction.

2. *Diarrhea* is a common early symptom and, if repeated within an interval of a few months, or, if persistent or chronic, should have an intensive study to eliminate cancer of the large intestine. Mild diarrhea on first rising in the morning should be a cause for suspicion.

3. *Constipation* and *obstipation* arising anew must receive similar consideration.

4. *Mucus* and *blood* in the stools invariably must receive an adequate explanation. If attended by painful and too frequent bowel movements, they constitute dysentery. If a specific cause, as, for instance, *Endamœba histolytica*, *Balantidium coli* or *Bacillus dysenteriæ*, is found and properly treated with no relief or only temporary relief of symptoms, further studies, including Roentgen ray, especially after barium enema, should be instituted promptly, and cancer should be diagnosed or consciously excluded.

5. *Tumor* may be the first sign, especially in the cecal region.

6. *Constitutional symptoms* of anemia, asthenia and loss of weight usually develop slowly, but in the 4 cases here reported, loss of weight was among the earliest symptoms noted.

7. *Persistent indigestion or changed bowel habit* in a person previously free of symptoms should excite suspicion.

In general, obstruction is usually seen in the annular, more scirrhous type of cancer in the descending colon and sigmoid, while toxic and constitutional symptoms are prone to attend cecal cancer.

Special Diagnostic Procedures. (In order of importance.) 1, Sigmoidoscopic examination should invariably be made but will not always be helpful, especially with cancer at or above the sigmoid flexure. If scirrhous cancer is present, there may be little or no change in the mucous membrane of the colon. Resistance to passage of the sigmoidoscope may be noted at or above 15 cm.

2. Barium enema and Roentgen ray examination localize the tumor and show the extent of involvement. It is most important to have the patient empty the bowel of barium and retake the Roentgen ray as an aid in early diagnosis.

3. Gross and microscopic fecal examination, for cellular, bacterial, chemical and food elements. Exhaustive search for protozoa is imperative.

4. Biopsy and study of histologic sections of masses found on sigmoidoscopic examination.

Case Reports. CASE 1.—(April 4, 1934.) Mrs. G. L. H., aged 49, widow, for 15 years has traveled constantly in South America, Asia and the Far East. Her previous history was not significant. The *present illness* began in 1924 as generalized abdominal pain, flatulence and bloating. In 1926 the condition was finally authoritatively diagnosed as amebiasis. At that time she received emetin and chiniofon. She has had frequent recurrences and exacerbations up to now. The stools showed blood, mucus and pus most of the time. During exacerbations she was treated and relieved repeatedly by emetin and chiniofon. One year ago, the picture gradually changed with an increased severity and localization of the pains in the upper left abdomen. Dysentery continued. Amebas were found no more. Relief did not follow the use of emetin and chiniofon. The patient lost 18.1 kilos in weight, and felt herself losing in strength and general vigor. Six weeks ago anemia was noted for the first time. Three months ago while in the Orient she suffered an attack which was probably due to partial obstruction of the colon.

Examination showed considerable pallor and evidence of wasting. There was tenderness under both costal margins, with no visceral enlargements. Varices of the legs were apparently of many years' duration. The blood pressure was a low normal and the pulse rate increased, results of anemia, weakness, and probably long use of emetin.

Laboratory Results. Urine, normal. *Blood count:* red cells 3,000,000; hgb. 9.7 gm.; white cells 18,920, with 79% neutrophils, 15% lymphocytes; 4% monocytes; and 2% eosinophils. *Stools* showed cysts of *Endolimax nana* and active trichomonads. Exhaustive search failed to reveal *E. histolytica*. *Stool culture* showed no growth of non-lactose fermenters of either the typhoid or dysentery groups. *Blood Wassermann* and *Kahn* tests were

negative. *Blood agglutinations* were negative for *B. dysenteriæ* of all types, typhoid and paratyphoids, brucella, and *B. enteritidis*. *Blood sugar* was 123 mg.; blood calcium 10.1 mg. per 100 cc.

Roentgen ray examination with barium enema showed an initial spasticity of the upper sigmoid region which later filled out normally. The rising barium column met with a fixed irregularity in the splenic flexure at a point corresponding with the painful point noted by the patient. Barium passed through this narrow ragged region, causing the patient considerable distress. The proximal colon had a normal appearance. The Roentgen ray conclusion was that the appearance favored neoplasm, but did not exclude an intrinsic lesion or granuloma of the bowel wall.

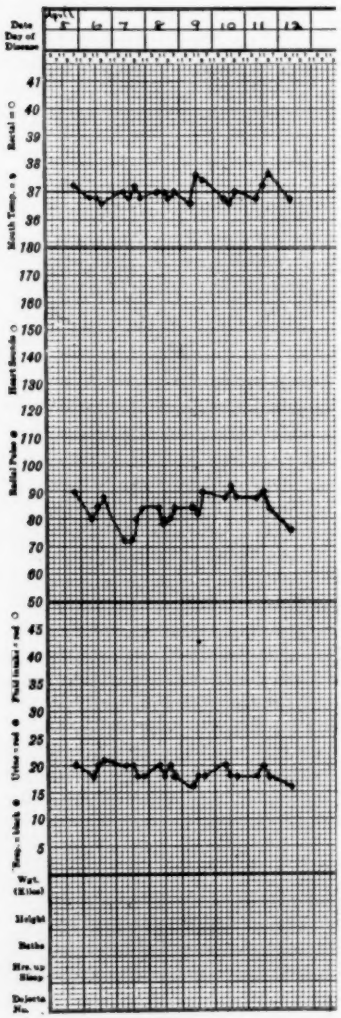

FIG. 1.—Case 1. Pre-operative chart.

Temperature, pulse and respiration are seen on accompanying chart.

Diagnosis. 1, Lesion of splenic flexure, probably carcinoma, possibly amebic granuloma; 2, secondary anemia and malnutrition; 3, history of about 9 years of amebic colitis, ending within the past year.

Subsequent Course. The patient was given 1 grain (0.065 gm.) of emetin hydrochlorid hypodermically daily for a total of 5 grains (0.33 gm.). This was followed by chiniofon which, however, caused serious colic and diarrhea, and was stopped after 10 doses. Vioform (0.5 gm. twice daily by mouth) was given to a total of 20 doses. It was felt that any amebic lesions would be controlled at least by this procedure, that a change in the Roentgen ray findings would be an indication of an amebic lesion rather than of malignancy, and that the risk of laparotomy would be reduced by removal of the whole or a large part of the amebic hazard. The pain decreased. The patient showed much weakness, with a pulse of 90 and blood pressure of 110/70. There was no significant change in the blood count. After the termination of the anti-amebic treatment noted the barium enema was repeated 3 weeks subsequent to the first Roentgen ray examination. The conclusion was that the same lesion was present unchanged. A definite diagnosis of carcinoma of the splenic flexure was made at this time.

One week later laparotomy (Dr. H. Glenn Bell) revealed a tumor of the splenic flexure with no evidence of metastasis. The left lobe of the liver was greatly enlarged and hepatic adhesions were found, indicating old

extensive hepatitis. The spleen was very small. The colonic mass was 6 by 5 cm. in area, involved the wall of the colon and was characteristic of carcinoma. A lateral colon anastomosis was done, short-circuiting but not closing off the splenic flexure and tumor. The patient went through a stormy convalescence protracted by a wound infection, and pneumonia of the left lower lobe. She finally left the hospital in fairly good condition, 52 days after the operation.

She was readmitted 15 days later for the second laparotomy and resection. Her blood count was now hgb., 5.2 gm.; 2,520,000 red cells; 11,600 white cells with 73% neutrophils. The urine was normal. After transfusion, the tumor was resected by Dr. Bell. The hemoglobin dropped to 3.4 gm., 5 transfusions followed, and a fecal fistula developed which closed after about 2 months. The tumor was removed by cautery. Again no evidence of metastasis could be found. The bowel was closed by end-to-end anastomosis. Convalescence was protracted and eventful, the patient finally being discharged in good clinical condition. She remained well for 9 months following removal of the tumor. The pathologic diagnosis of the tumor by Dr. James F. Rinehart was adenocarcinoma of the large intestine. A thorough check-up 5½ months after operation showed normal stool analysis with no amebas or other parasites except trichomonads. The blood count was hgb. 13.1 gm. and 3,840,000 red cells. The patient died suddenly 10 months after operation from an apparent recurrence of the carcinoma at the splenic flexure, though autopsy was not obtained.

Case 2.—E. F. B., aged 49, widower, when first seen on March 10, 1933, complained of blood in the stools for 1½ years past. He had lost 52 pounds in that time. Bowels moved 3 to 4 times daily. Nausea and vomiting were absent. Looseness of the bowels had been noticed for some 4 years, with increasing pain and colic. His other complaints were increasing weakness and nervousness.

His previous medical history was limited to excessive use of tobacco and considerable recurring dental infection. He was born in Nebraska, was never outside the U. S. A., and had lived in San Francisco for the past 32 years.

Examination showed a pale, lethargic man with evidence of wasting. The blood pressure was 90/58, with a pulse rate of 80. The abdomen was relaxed. The sigmoid was cordlike and tender, and a boggy cecum could be felt. The liver was somewhat enlarged and tender.

Laboratory Findings. Urine was normal. Blood count showed 80% neutrophils, 31% lymphocytes, 3% mononuclears and 1% eosinophils; red cells 4,650,000. *Stools* exhibited much blood and mucus but no parasites were seen. Sigmoidoscopic examination showed a normal mucosa with some gray mucus high up which contained abundant motile *E. histolytica*. Roentgen ray examination by barium enema was reported by Dr. I. S. Ingber as follows: "The colon fills normally. There is no evidence of an organic lesion."

Diagnosis. Amebic colitis, with possible amebic hepatitis. Hypotension.

Treatment consisted of 8 courses (5 gm. each) of carbarsone by mouth, 1 course rectally, and 3 courses (5 gm. each) of vioform over a duration of 9 months. There was excellent clinical improvement with a weight gain to 168 pounds. After cessation of treatment, amebas were not found on repeated examinations and the patient was able to return to hard work.

On August 7, 1934, 8 months after termination of treatment, he complained of occasional colic and blood in the stools. No amebas were found. He was relieved of the colic by omitting coffee and tea. After 2 weeks, abdominal pain became severe, especially in the hypogastrium and on the left side. The abdomen was excessively tender and a hard mass was pal-

pable deep in the lower left quadrant, apparently arising in the sigmoid. Sigmoidoscopic examination was negative. Barium enema Roentgen ray showed an obstruction in the lower sigmoid, allowing filling only of the rectal ampulla. The pre-operative diagnosis was abscess, amebic granuloma, or new growth.

FIG. 2.—Case 2. Pre-operative chart.

Laparotomy was performed by Dr. Dudley Smith who found a mass the size of a large orange involving the sigmoid colon, fixed, hard and inseparable. Cecostomy and colostomy were done. Postoperative diagnosis was cancer of the sigmoid, inoperable. Ten months after operation, the patient was still relieved of obstructive symptoms but his general condition was failing.

CASE 3.—J. B. F., male, aged 40, was first seen February 4, 1935. *Present illness* began 7 years ago in Los Angeles as a diarrhea with occasional blood in the stools. There was no pain and no fever. *Endamœbæ histolyticæ* were found and have been present at various times up to 1 month ago in spite of treatment. Therapy has been varied and nearly

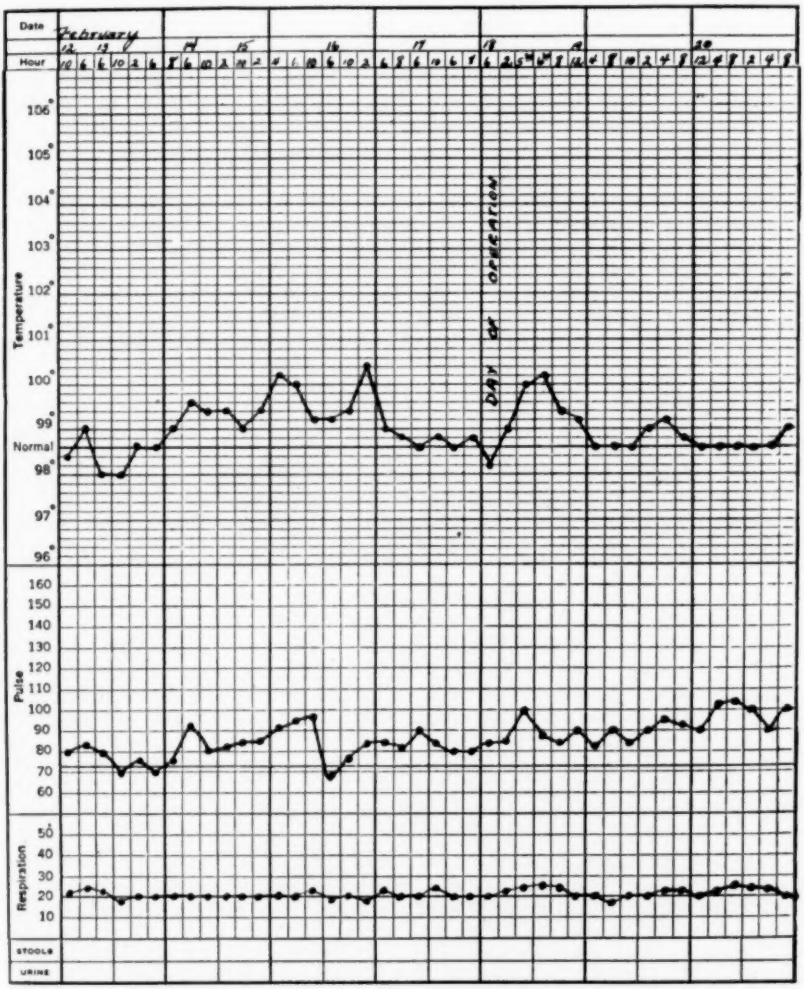

FIG. 3.—Case 3. Pre-operative chart.

constant, including a gall-bladder drainage, emetin courses, acetarsone over a period of 2 years, chiniofon, autogenous vaccines, tannalbin, and finally carbarsone. He has noted an intolerance for carbohydrates which cause diarrhea with foamy stools. Symptomatic temporary relief always follows administration of carbarsone. Barium enema Roentgen rays by Dr. L. T. Stephens, Seattle, November 16, 1932, gave the following conclusions:

"Barium enters rectum normally, which is small and does not dilate. Barium passes up rapidly through a tortuous narrow descending colon with complete absence of haustration. In the middle half of the descending colon on external surface are a number of small protuberances. On the opposite side over midportion of ileum is a much larger protuberance. These protuberances suggest ulcers. Barium passes rapidly across transverse colon, rapidly into cecum and small bowel. Lower bowel is remarkable for absence of haustration. No constricting bands were visualized in region of ileum or cecum. Conclusion: Spastic ulcerated colon."

Past History. The patient's father died with chronic arthritis at 61 years, and one brother now has chronic arthritis.

The patient was born in Manitoba, and since the age of 3 has lived on the Pacific Coast of the United States, with trips to New Orleans and Tia Juana. He had all the usual childhood diseases, and diphtheria at 15 with a history of cardiac involvement. When taking emetin, he has noticed mental slowing and weakness and pains in the lower extremities. Lately he has noticed dyspnea on exertion, pronounced weakness and had a fainting spell 1 week ago. He is abstemious in diet and habits, uses no alcohol or tobacco, and cannot take coffee because of its laxative effects. His weight has dropped from a normal of 150 pounds to 136 pounds.

Examination showed moderate pallor, evident weakness and poor muscle tone. The heart was not enlarged, blood pressure 110/70 (Tycos) with no murmur but a tendency to increased rate (80 to 88).

Laboratory Findings. Urine, normal. *Blood count*, moderate secondary anemia only. *Stools*, no amebas on repeated search. A few Charcot-Leyden crystals, many red blood cells, moderate mucus, many short-chained streptococci. *Blood Wassermann* and *Kahn* tests were negative. Blood calcium, 8 mg. per 100 cc.

Electrocardiogram. Rate 63.. Normal rhythm. Slightly slurred R in II and III, and of S in II and III. *S–T* interval elevated in III. Suggests myocardial damage.

Roentgen ray examination of the *abdomen* by Dr. R. F. Kile gave the following summary: The colon is fairly well outlined, possibly due to previous medication, such as bismuth powders. No abnormality or distention of the bowel is noted. The liver is not enlarged and there is no evidence of a subdiaphragmatic abscess. The right kidney shadow is well defined and the psoas shadow is normal, which would rule out the possibility of an abscess about the kidney.

Barium enema shows a marked constricted area at the rectosigmoid junction which is approximately 4 inches in extent. The channel through this portion of the bowel is less than a cm. in diameter. Throughout the entire descending, transverse, ascending, cecum and terminal ileum, there is marked irregular filling with many areas suggesting ulceration.

Conclusions. Ulcerative colitis, which involves the entire colon and terminal ileum, constricting an area of sigmoid, suggesting an inflammatory mass.

Diagnosis. Amebic colitis beginning 7 years previously, and eventually cured. Carcinoma of sigmoid with partial obstruction and probable metastases.

Operation (Dr. I. W. Thorne, February 18) revealed an inoperable carcinoma of the sigmoid, with metastases in the mesentery of the small intestine. A permanent cecostomy was done. Death ensued on March 31, 1935.

Necropsy (Dr. Z. E. Bolin). *Anatomic Diagnoses.* 1, Adenocarcinoma arising in the sigmoid colon with extension to the sigmoid mesentery, retroperitoneal lymph nodes, first, third and fourth lumbar vertebræ; with

metastases to the peritoneum, diaphragm, both pleural cavities, pleura of both lungs, liver, gall bladder and pericardium; 2, bilateral pleural effusion, carcinomatous in origin, right 200, left 500; 3, pericardial effusion 100 cc.; 4, marked emaciation; 5, dilatation of the heart with brown atrophy; 6, chronic passive congestion of the viscera; 7, abscess right parietal region extending from the base of the skull to the clavicle, staphylococci and B. coli in origin; 8, cecostomy opening; 9, acute splenic tumor; 10, edema of lungs, slight; 11, generalized arteriosclerosis.

CASE 4.—B. A. B., male, aged 48, was first seen April 3, 1933, complaining of loose bowel movements with blood in stools and loss of 23 pounds in weight during past year. The symptoms began with diarrhea and bleeding external hemorrhoids 3 years ago. For 2 years these were only symptoms. During the past year, blood has been increasingly frequent in the stools, associated with much mucus and at times some colic. He has been passing about 10 to 14 loose stools each day. The hemorrhoids had disappeared. Lately he has had pain under and above the right costal margin.

His mother died at 72 years of a stomach tumor. He was born in Nebraska and always lived in the States between Nebraska and Northern California. He was a rancher until 12 years ago when he became a high school teacher. For years he had worn a truss over a right inguinal hernia. In 1921, "flu" with hemoptysis led to suspicion of phthisis which was never confirmed. He had had pleurisy at one time.

Examination showed a thin abdomen with palpable, hard, tender sigmoid and descending colon. The cecum was thickened and hard. The liver edge was 4 finger breadths below the costal edge, smooth, and tender in the region of the gall bladder. There was no jaundice. The only other abnormal finding was inequality of the pupils. Sigmoidoscopic examination to a depth of 22 cm. showed an intensely congested mucosa with a few superficial ulcers high in the rectal ampulla. There was much adherent gray mucus.

Laboratory Findings. Urine, normal. *Wassermann* and *Kahn* tests, negative. *Phenolsulphonphthalein* excretion, 35% in 2 hours. *Blood count:* Red cells 3,520,000; hgb. 13.2 gm.; white cells 6920; neutrophils 64%, lymphocytes 27%, mononuclears 4%, eosinophils 2% and basophils 3%. *Stools* showed motile *E. histolytica* with much blood and mucus.

Diagnosis was made of amebiasis, hepatitis (possibly amebic), amebic colitis and secondary anemia.

Treatment for the amebiasis consisted of carbarsone (10 gm.) and vioform (7.5 gm.) for 1 month with dietary control, vitamin B and bismuth subcarbonate. Symptoms improved, the liver pain disappeared and he gained 8 pounds in weight. Amebas were not found again on repeated search. The liver retreated within 2 finger breadths of the costal edge.

Further Course. Improvement was temporary and in spite of the absence of amebas, diarrhea easily recurred, at times with some blood. In an effort to insure that amebiasis was not responsible further for the condition, emetin hydrochlorid was given hypodermically, 1 grain (0.065 gm.) daily for 5 days. No change in symptoms followed. Roentgen ray of the colon with barium enema on April 27 showed marked spasm of the lower descending colon and sigmoid which was reported as irregular in character and having the characteristics of inflammatory induration rather than of neoplasm.

Examination showed apparent improvement in the abdominal condition. The colon was not palpable nor tender. The liver descended 2 finger breadths only, was smooth, firm and not tender. No jaundice was present. There was some edema of the legs. Symptomatic colonic treatment with bed rest gave clinical improvement. On May 29, abdominal pain, nausea and watery diarrhea appeared, followed by sudden severe pain over the

liver area. The white cell count rose to 15,520. There was no fever. Roentgen ray studies showed normal lung fields and heart contour, with a limited mobility of right diaphragm and marked enlargement of liver. There was no definite evidence of liver abscess. Improvement again took place. On recurrence of symptoms 2 weeks later, gastro-intestinal Roentgen

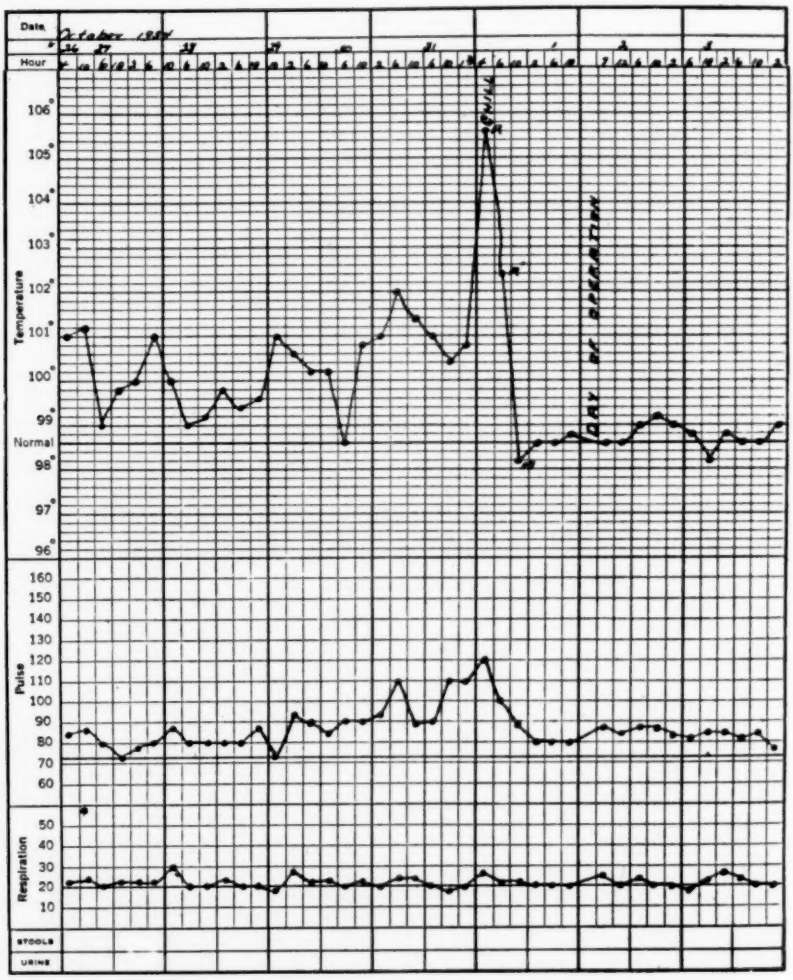

FIG. 4.—Case 4. Pre-operative chart.

rays by Dr. R. F. Kile gave the following reading: "Lung fields are clear. Heart shadow not enlarged. Spastic antrum and deformed bulb seemed rather characteristic of gall-bladder disease. The irregular filling of the rectal ampulla and sigmoid, while rather extensive, has the characteristics of a new growth." Laparotomy by Dr. Alanson Weeks showed a fixed

FIG. 5.—Case 1. Pre-operative Roentgen ray of colon with barium enema.

FIG. 6.—Case 2. Pre-operative Roentgen ray of colon with barium enema.

FIG. 7.—Case 3. Pre-operative Roentgen ray of colon with barium enema

FIG. 8.—Case 4. Pre-operative Roentgen ray of colon with barium enema.

tumor of the sigmoid, 2½ inches across, and numerous hard, irregular masses in the substance of the liver. Sigmoidostomy was done to relieve obstruction.

Diagnosis. Carcinoma of sigmoid with metastases to liver. Inoperable. The patient died 6 months later, without necropsy.

SUMMARY OF CASES.

Case			Duration of Amebiasis	Residence.	Previous anti-amebic treatment.
1	G. L. H.	F., 49	10 yrs.	U. S., Europe, Far East	Late + + + + Emetin poisoning.
2	E. F. B.	M., 49	4 yrs.	Neb. and Calif.	None, undiagnosed.
3	J. B. F.	M., 40	7 yrs.	Pac. Coast, U. S.	Early + + + + Emetin poisoning.
4	B. A. B.	M., 48	3 yrs.	N. West, U. S.	None, undiagnosed.

Discussion. In all cases, the amebas were finally eradicated, but symptoms persisted, recurred or were intensified. In Cases 2 and 4, amebiasis had been unsuspected and untreated. In Case 1, amebiasis was discovered late and overtreated, resulting in emetin poisoning. The same result followed overtreatment early of Case 3. These 2 cases probably belong in the residual 5% of amebiasis which are resistant, require adjuvant surgical treatment or even for practical purposes are incurable.

All cases of chronic amebiasis with present or recurring dysentery or diarrhea should have Roentgen ray examination including barium enema, in order to determine early, if possible, the extent of amebic damage to the bowel and, more important, to ascertain evidence of malignancy. Certainly one should weigh the amebic factor and the patient's response to this infection against possible carcinoma superimposed upon an amebic colitis.

A careful review of such cases as No. 3 above shows the easy development of non-amebic ulcerative colitis and raises certain questions of clinical importance. Is there some predisposing factor which facilitates the development of chronic ulcerative colitis and cancer, as a sequel and complication of amebiasis? Do vitamin G and the intrinsic gastric hormone play a part in this predisposition? Is there a relationship here to the frequently noted importance of high vitamin diet in the treatment of amebiasis[10]? Does the course of the disease and the eventual occurrence of malignancy, or the obscure chronic increasing lesions of amebiasis depend on or have relation to, deficiency of vitamin G, or vitamin B? Do these same factors have any bearing on the sequential relation of cancer to amebiasis? The answers to these questions must include due consideration of the at present unexplained variations in the course of the disease produced by *E. histolytica*, variable relations between

ameba and its bacterial camp followers, and especially on the factors that make up normal resistance of the healthy colon.

Cancer may follow amebiasis by at least two known pathologic methods. (1) Chronic irritation may arise from the amebic lesion or its products, or from reactive or adventitious tissue secondary to the amebic lesion. Such irritation would be most marked at the sites of election for amebic colonization which, as has been noted, coincide with the favorite cancer areas. This does not mean that the amebic lesion is entirely responsible for such irritation inasmuch as the cancer areas are the same in non-amebic cases. It may well mean that the amebic lesions, in the presence of poorly understood predispositions, increase the facility of cancerous transition. (2) The ease with which polypoid and adenomatous growths follow amebic lesions in the colon and rectum, offers a definite added hazard because of the known ease with which such benign growths undergo cancerous change.

Summary. Four cases of amebiasis are presented, in which carcinoma of the colon followed and accompanied the amebic infection. The coincident sites of election and an overlapping of symptoms often make the differential diagnosis difficult. In at least two ways, amebic lesions may institute changes leading to cancer: by chronic irritation and by production of benign adenomas and polyps which easily become cancerous. A problem needing solution relates to possible predisposing factors which may favor development of cancer in cases of amebiasis.

REFERENCES.

1. Trousseau's Clinical Medicine, Trans. by Cormack, Ed. of 1868, London, 1871, New Sydenham Society, IV, 182.

2. Desjardins, M. A.: Les pseudo-cancers coliques d'Origine Amibienne, Bull. et mém. Soc. de chir. de Paris, **21**, 443, 1929.

3. Gunn, H., and Howard, N. J.: Amebic Granulomas of the Large Bowel, J. Am. Med. Assn., **97**, 166, 1931.

4. Rogers, L.: Recent Advances in Tropical Medicine, 2d. ed., 1928, Philadelphia, Blakiston & Sons Co., p. 251.

5. Hines, L. E.: A Form of Polypoid Colitis, a Late Stage of Amebic Dysentery, J. Am. Med. Assn., **81**, 12, 1923.

6. Kaufmann, E.: Spezielle pathologische Anatomie, **1**, 512, 1911, Berlin, Walter de Gruyter & Co.

7. Tuttle, J. P.: Diseases of Anus, Rectum and Pelvic Colon, 2d ed., p. 762, 1907, New York, D. Appleton & Co.

8. Clark, H. C.: The Distribution and Complications of Amebic Lesions Found in 186 Postmortem Examinations, Am. J. Trop. Med., **5**, 157, 1925.

9. Anderson, H. H., and Reed, A. C.: Amebophobic Hazards (to be published).

10. Reed, A. C.: The Treatment of Amebiasis, J. Am. Med. Assn., **103**, 1224, 1934.

PRODUCTION OF NEPHRITIS IN DOGS BY ROENTGEN RAYS.

By Irvine H. Page, M.D.,
ASSOCIATE IN MEDICINE, ROCKEFELLER INSTITUTE, NEW YORK CITY.

(From the Hospital of the Rockefeller Institute for Medical Research.)

Irritation of kidneys by means of Roentgen rays to produce nephritis is a procedure which has been employed by a number of investigators.[1–8] The manner in which it has been applied has varied. Most workers[1–6] have exposed the kidneys by surgical operation and irradiated them directly with medium wave length Roentgen rays. The disadvantage of this method is that treatment is usually limited to one dose and is a very drastic one. Others[8] have exposed them to high voltage Roentgen rays applied through the abdominal wall. In this manner infection of the kidneys is avoided, but irradiation is not limited to them. We have employed the method of Page,[9] in which the kidneys are transplanted to a position directly beneath the skin of the loin. After healing occurred the organs were irradiated with relatively small, repeated doses of Roentgen rays. This method has the advantage that the severity of injury may be more precisely regulated and irradiation limited to the kidneys. Simultaneous with the operation of renal transplantation, the carotid artery was sewn within a flap of skin of the neck (van Leersum method), enabling one to measure arterial blood pressure.

Method. Medium sized dogs (12 to 20 kg.) were anesthetized with amytal (isoamylethyl barbituric acid 65 mg. per kg. body weight). About 2 inches of the common carotid artery was separated from the surrounding tissues and sewn within a flap of skin. The wound beneath the loop was closed with catgut (No. 1). Collodion was poured on the wound edges and a dry cotton dressing applied. A kidney was then exposed through a lumbar incision and separated from perirenal fat without entering the peritoneal cavity. A pocket was made in the subcutaneous tissue, the kidney placed within it and the muscle layers closed beneath it with No. 1 chromic catgut. Ample space was allowed for the renal pedicle. The skin was then sutured over the kidney. This procedure was repeated on the opposite kidney. Healing of the wounds occurred usually by primary intention with 14 days. In some dogs one kidney was removed and the other transplanted. The renal pedicle was stripped of nerves in other dogs as described by Page.[9]

After a control period of about 3 weeks, during which blood pressure measurements and chemical examinations of the blood and urine were made, the dogs were anesthetized with amytal and each kidney irradiated. The irradiation was performed by Miss Christine MacDonald, as follows: The hair over the kidneys was shaved and they were carefully blocked off with sheets of lead. Two erythema doses were applied to each kidney, 26 minutes being required for each dose. A 130 kilovolt peak, 5 milliamperes, 3 mm. aluminum filter at 30 cm. distance, was employed. Most of the animals received from 5 to 7 erythema doses upon each kidney during a period of from 6 to 21 weeks.

Blood urea was ascertained by the gasometric hypobromite method of

Van Slyke and Kugel,[10] hemoglobin by the oxygen combining capacity of Van Slyke and Neill,[11] plasma proteins by Howe's method,[12] and plasma lipids by the gasometric method of Kirk, Page and Van Slyke.[13] Samples of blood were taken from the femoral artery after 24 hours fasting, but with liberal allowance of water. Heparin was used as anticoagulant. The dogs were fed the usual laboratory diet consisting of ground meat, bone and dog biscuits, throughout the experiment.

Results. Recovery from the operations of renal transplantation and preparation of the carotid loop was uneventful. Measurements of blood pressure, taken usually every 2 days for periods of about 3 weeks, showed marked variations in different animals, some being as high as 196 mm. of mercury. The pressure of individual animals seldom altered more than 40 mm. The average ranged from 120 to 170 mm. After each dose of Roentgen rays the dogs lost their appetite for a day or two but soon regained it. Their health became poor following administrations of from 4 to 6 erythema doses to each kidney. Loss of weight, loss of appetite and weakness were the most obvious signs. The urine contained protein, casts, and occasionally red blood cells. The irradiated kidneys became progressively smaller until, in some cases, they were not larger than a large walnut. The terminal stage was ushered in by vomiting, oliguria, blood in the feces and complete loss of appetite. During the last few days the dogs would not even take water. Muscular twitching was often observed. Breathing often became similar to that observed during acidosis. In one animal in which the serum CO_2 was measured one day before death, it was found to be 10.99 millimoles per liter. Some of the animals became comatose while others were conscious until within a few hours of death. During the stage of uremia, arterial blood pressure fell to 60 mm. or lower.

Autopsy showed that the kidneys were markedly shrunken, and in rare cases the capsule stripped with difficulty, leaving a scarred surface. The cortex was thinned and glomeruli could be seen. Some areas were almost completely obliterated by scar tissue. A description of the microscopic findings will not be presented, as it has already been done by Hartmann, Bollinger and Doub,[5] and more extensively by Earlam and Bollinger.[6,7] Dr. C. P. Rhoads states that the most characteristic lesion observed by him in sections of the kidneys of our dogs was hyalin necrosis of Henle's loops and proliferation of new epithelium. There was an increase in interstitial connective tissue apparently due to occlusion of the terminal bloodvessels. There was also a suggestion of proliferation of the nuclei of the glomerular capillaries with edema and thickening of the capillary wall. Dr. Rhoads has prepared a photograph which illustrates in a general way the lesions produced in our dogs.

Arterial blood pressure became somewhat elevated after irradiation in 5 of 7 dogs in which it was measured, provided the dogs were not approaching the terminal stage (Table 1).

TABLE 1.—CONSTITUENTS IN 100 CC. OF BLOOD FROM FASTING DOGS WHOSE KIDNEYS WERE TREATED WITH ROENTGEN RAY.

Dog No.	Total lipid carbon, mg.	Total lipid, mg.	Cholesterol			Lipid amino N, mg.	Total lipid N, mg.	Lipid P, mg.	Total phosphatide, mg.	Urea N, mg.	Hemoglobin vol. % O_2 capacity	Plasma proteins, %	Operation on the kidneys, other than renal transplantation	Time blood was taken before death, days	Average blood pressure mm. Hg		Erythema dose of Roentgen ray.	Time before death after beginning treatment, weeks.
			Total, mg.	Ester, mg.	Free, mg.										Before operation.	After operation.		
51	540	722	106	50	56	5.8	27.2	14.6	343	21.2	23.7	8.07	None	42	144	170	6	6
	782	1026	212	..	..		59.6	21.8	512	71.6	24.8	9.41	None	1				
41	462	601	72	36	36	12.6	31.2	15.4	362	16.2	14.3*	7.26	None	49	160	210	6	13
	710	923	172	115	57	8.7	55.8	15.7	369	134.4	17.4	6.94	None	5				
7	1226	1594	286	179	107	9.0	54.0	16.5	388	150.2	28.2	....	Nephrectomy denervation	2 hrs.	164	180	5	12
11	1013	1317	320	196	124	23.0	114.3	20.8	489	301.8	26.1	....	Nephrectomy denervation	1	120	122	4	7
21	469	610	203	131	72	14.1	64.0	7.4	174	158.5	..	..	None	..	140	172	8	21
23	454	590	103	46	57	3.7	11.9	8.7	204	58.2	..	..	None	35	136	148	8	9
	589	766	..	..	..	..	..	..	..	94.5	..	..	None	20				
	756	983	216	..	..	..	..	..	..	174.3	23.1	..	None	5				
1	371	482	148	76	72	6.9	33.2	6.4	150	..	..	7.38	Nephrectomy	5	170	200	5	9
Control	611	794	165	70	95	6.2	4.4	13.9	327	..	..	..	Both kidneys denervated	..	196			
Control	875	1137	152	36	116	7.8	6.5	20.6	484	..	..	..	Both kidneys denervated	..	154			
Control	540	702	170	108	62	5.8	..	18.0	423	10.6	19.0	..	Normal	..	130			
Control	663	861	194	124	70	5.8	38.1	18.2	428	13.6	18.7	7.25	Unilateral nephrectomy	..	136			

* Low value probably due to blood loss during operation.

Observations on some chemical changes in the blood were made (Table 1). Hemoglobin was increased somewhat, especially during the terminal stage. Probably this was due to hemoconcentration, since the plasma proteins also rose (Dog 51). Nephritis produced by Roentgen rays differs sharply in this manner from Bright's disease in human beings, for in the latter anemia is one of the most characteristic signs.

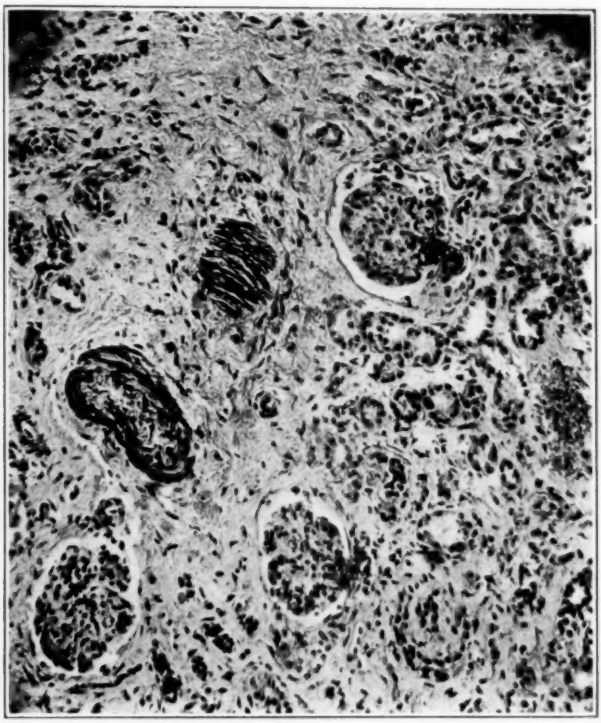

FIG. 1.—Section of dog's kidney treated with Roentgen rays showing interstitial sclerosis, avascular glomeruli with nuclear proliferation, cell rests representing tubules which have atrophied, and perivascular sclerosis.

The urea nitrogen rose in all the animals, especially during the terminal few weeks. In one (No. 11) it reached the very high value of 302 mg.%.

The behavior of the plasma lipids was similar to that observed in patients suffering from the terminal stage of chronic hemorrhagic Bright's disease found by Page, Kirk and Van Slyke.[15]

Except in those dogs where marked hemoconcentration had occurred, the total lipids, total ester and free cholesterol and lipid phosphorus did not differ from normal dogs on the same diet. Where marked concentration of the blood occurred (Nos. 7 and 11)

total lipid, total free and ester cholesterol, and lipid amino nitrogen were moderately elevated. Just as in human blood, as observed by Van Slyke, Page, Kirk and Farr,[14] dogs' blood contained a substance (or substances) which is soluble in petroleum ether, containing amino groups in greater proportion to phosphorus than the 1 to 1 ratio present in cephalin.

The total lipid nitrogen rose markedly, but not parallel with the rise in urea nitrogen. For example, one analysis showed urea nitrogen to be 72 mg. %, and lipid nitrogen 60 mg. %, while another showed urea nitrogen 150 mg. %, and lipid nitrogen 54 mg. %. Lipid nitrogen evidently rises progressively during the course of renal insufficiency produced by Roentgen rays independently of urea nitrogen.

Summary. Chronic injury localized to the kidneys of dogs has been accomplished by transplanting the kidneys to the flank beneath the skin, and, after healing, irradiating them with Roentgen rays. The tissues lateral to the kidneys were protected by lead plates. Repeated doses of Roentgen rays have been given in order to secure chronic, progressive lesions. These lesions have been described adequately by others,[5–7] and consist largely, as we can confirm, of tubular damage with usually less extensive glomerular changes. Nephritis produced in this manner leads to death in the course of a few months, with symptoms typical of renal failure.

The following changes in the chemical composition of the blood have been noted: Slowly progressive but independent rise in urea nitrogen and total lipid nitrogen, and maintenance of total lipids, total, free and ester cholesterol, lipid amino nitrogen and lipid phosphorus, within limits normal for dogs on the same diet. These data closely resemble those found by Page, Kirk and Van Slyke[15] to be typical of the terminal stage (urea clearance less than 20% of normal) of hemorrhagic Bright's disease in man. They differ in that hemoconcentration occurred in the dogs with a corresponding increase in plasma proteins, hemoglobin and, to a less marked degree, the plasma lipids. They differ further in that anemia, which is regularly observed in human nephritis, did not occur in the dogs with Roentgen ray nephritis.

Just as in human blood, dog's blood contains substances, soluble in petroleum ether, containing amino groups in greater proportions in phosphorus than the 1 to 1 ratio present in cephalin.

REFERENCES.

1. Linser, P., and Helber, E.: Experimentelle untersuchungen über die Einwirkung der Röntgenstrahlen auf das Blut und Bemerkungen über die Einwirkung vom Radium und ultraviolettem Lichte, Deutsch. Arch. f. klin. Med., **83**, 479, 1905.

2. Buschke, A., and Schmidt, H. E.: Ueber die Wirkung der Röntgenstrahlen auf Drüsen, Deutsch. med. Wchnschr., **31**, 495, 1905.

3. Schultz, O. E., and Hoffmann, R. St.: Zur Wirkungsweise der Röntgenstrahlen, Deutsch. Ztschr. f. Chir., **79**, 350, 1905.

4. O'Hare, J. P., Altnow, H., Christian, T. D., Calhoun, A. W., and Sosman, M. C.: Chronic Nephritis Produced by *X*-ray, Boston Med. and Surg. J., **194**, 43, 1926.

5. Hartmann, F. W., Bolliger, A., and Doub, H. P.: Experimental Nephritis Produced by Irradiation, Am. J. Med. Sci., **192**, 487, 1926.

6. Bolliger, A., and Earlam, M. S. S.: Experimental Renal Disease Produced by *X*-rays; Production and Functional Study of Standardized Lesion, Med. J. Australia, **1**, 340, 1930.

7. Earlam, M. S. S., and Bolliger, A.: Experimental Renal Disease Produced by *X*-rays; Late Results of Irradiation, Ibid., **1**, 826, 1932.

8. Krause, P., and Ziegler, K.: Experimentelle unterusuchungen über die Einwirkung der Röntgenstrahlen auf tierisch Gewebe, Fortschr. a. d. Geb. d. Röntgenstrahlen, **10**, 126, 1906–1907.

9. Page, I. H.: Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, Am. J. Physiol., **112**, 166, 1935.

10. Van Slyke, D. D., and Kugel, V.: Improvements in Manometric Micro-Kjeldahl and Blood Urea Methods, J. Biol. Chem., **102**, 489, 1933.

11. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, Ibid., **61**, 523, 1924.

12. Howe, P. E.: The Determination of Proteins in Blood—a Micro Method, Ibid., **49**, 109, 1921.

13. Kirk, E., Page, I. H., and Van Slyke, D. D.: Gasometric Microdetermination of Lipids in Plasma, Blood Cells and Tissues, Ibid., **106**, 203, 1934.

14. Van Slyke, D. D., Page, I. H., Kirk, E., and Farr, L. E.: Nature of Nitrogenous Constituents in Petroleum Ether Extract of Plasma, Proc. Soc. Exp. Biol. and Med., **32**, 837, 1935.

15. Page, I. H., Kirk, E., and Van Slyke, D. D.: Plasma Lipids in Essential Hypertension, J. Clin. Invest., Plasma Lipids in Chronic Hemorrhagic Nephritis, Ibid, 1935.

CREATINURIA IN ADULT MALES.*

By F. H. L. Taylor, Ph.D.,

CHEMIST, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL; RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL,

AND

W. B. Chew, M.D.,

ASSISTANT RESIDENT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL; RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

The presence of creatin in the urine of children in the prepuberty period and of normal adult women has been a generally accepted fact. Its occurrence in the urine of normal adult males has not been so accepted. Folin and Dennis[1] reported its occurrence in the urine of a 17-year-old boy. Rose[2] and Harding and Gaebler[3] regard 15 to 16 years as the limiting age at which creatin fails to be normally excreted in the urine of males.

* The expenses of this investigation were defrayed in part by a gift from Smith, Kline & French Laboratories, of Philadelphia, to the Harvard Medical School.

In the course of investigations on the partition of the nitrogenous constituents of urine, during the past 3 years, the presence of creatin as determined by difference between preformed and total creatinin was found in the urine of both normal subjects and hospital patients, including a large number of adult males.

Our interest was further stimulated by the interesting papers of Light and Warren,[4] who report the occurrence of creatin in the urine of 35 out of a total of 81 boys between the ages of 14 and 19. These authors present data to show a diminishing incidence with age. The amount of creatin found in the 24-hour samples varied from 15 to 229 mg.

These observations of Light and Warren, together with our own experience led to a study of creatinuria in a group of somewhat older normal male subjects.

Experimental. Ten male medical students between the ages of 20 and 24, and 5 adult male members of the laboratory staff, were studied. All subjects were forbidden any *unusual* exercise but were allowed to carry on the daily routine in their usual way. No restrictions as to diet were made. A record of the diet was kept and in no instance was it at all unusual. All subjects were free from low-grade infections or diseases which might occasion an increased temperature or basal metabolic rate. No history of nephritis, cardiac disease, or muscular abnormality was present. The 24-hour urine specimen was collected over the usual preservative used in this laboratory of 10 ml. acetic acid and 5 ml. chloroform. Blank control experiments were run on reagents and preservative, and in later studies toluene and chloroform were substituted for the acetic acid-chloroform preservative to rule out any possible interference from this source.

Analyses for both preformed and total creatinin were made in duplicate on each urine by the method of Folin.[5] Both the methods of autoclaving and of boiling were used for the determination of total creatinin. Results by both the latter procedures checked consistently within the experimental errors of the two methods, *viz.*, approximately 10 mg. for the 24-hour sample. The results by boiling were always somewhat lower than those obtained by autoclaving.

From the results obtained (Table 1) it would appear that amounts

TABLE 1.—CREATINURIA IN NORMAL MALES.

Subject.	Age.	Weight, lbs.	Height, in.	Total nitrogen.*	Preformed creatinin nitrogen.*	Creatin nitrogen.*
T. T. H.	20	175	69.5	19.30	0.725	0.018
E. H.	21	148	69.0	16.08	0.669	0.591
L. G.	22	175	70.0	17.85	0.830	0.000
J. T. H.	22	170	73.0	15.45	0.756	0.071
H. P. P.	22	140	70.0	13.10	0.664	0.048
A.	22	146	70.5	13.58	0.645	0.043
H.	22	170	68.0	12.92	0.606	0.122
H. W.	22	140	70.0	16.35	0.491	0.010
C. N.	23	180	70.0	14.48	0.519	0.028
J. P.	23	155	75.0	15.45	0.748	0.025
T. H. H.	29	165	72.0	12.68	0.702	0.065
E. F.	29	165	71.5	13.08	0.695	0.057
W. B. C.	33	134	68.0	10.90	0.512	0.042
J. R.	30	120	65.0	11.28	0.531	0.058
F. H. L. T.	34	126	68.0	10.67	0.511	0.091

* All values expressed as gm. excreted in 24 hours.

of creatin varying between 10 and 100 mg. in 24 hours are present in the urines of most of the normal males in the group of 16 subjects studied. Variations in the amounts excreted by the group of the third decade are much wider than those of the fourth.

Data obtained on 3 patients, who were confined to bed at the time these observations were made, are given in Table 2. The same

TABLE 2.—CREATINURIA IN PATIENTS ABOVE 35 YEARS OF AGE.

Patient	Diagnosis.	Sex.	Date.	Remarks.	Total nitrogen, gm.*	Total creatinin nitrogen, gm.*	Creatin nitrogen, gm.*
D	Leukemia	Female	3/13/33	Elevated B.M.R.	11.00	0.299	0.112
			3/20/33		10.30	0.312	0.056
			3/22/33		9.22	0.297	0.000
W	Obesity	Male	5/31/33	Standardized diabetic diet. Limited exercise.	8.93	0.455	0.069
			6/ 2/33		11.55	0.576	0.060
			6/ 3/33		15.30	0.640	0.028
			6/ 5/33		13.40	0.567	0.038
			6/ 9/33		12.19	0.514	0.011
S	Addison's disease	Female	5/20/33	....	....	0.326	0.092
			5/21/33	....	....	0.284	0.032
			5/23/33	....	....	0.290	0.045
			5/26/33	....	....	0.289	0.028
			6/24/33	....	....	0.304	0.060
			6/25/33	....	....	0.318	0.058
			6/26/33	....	....	0.294	0.055

* All values expressed in gm. excreted in 24 hours.

precautions and technique were followed in every instance. It will be observed that the values for urine creatin nitrogen in the case of 2 female subjects are of the same order of magnitude as those found for normal males. It is of interest, also, that marked variations occur in the output of creatin from day to day. It is probable that, in subjects in whom no creatinuria is found, serial analyses would show the presence of this substance in variable amounts. Variations in the creatin nitrogen values of the 3 patients occurred during the time that they were confined to bed. It seems quite possible that had Light and Warren followed their subjects while confined to bed for a longer period of time they would have encountered considerable fluctuations in the amount of creatin excreted in the urine.

Table 3 shows the daily excretion of creatin in a normal male adult of 33 years at frequent intervals. The diet was uncontrolled except for the addition of a constant amount of nucleoprotein for other experimental purposes. The nucleoprotein used was repurified yeast nucleic acid which is not known to cause an increase of exogenous creatin. It is sufficient to remark here that the excretion of

other nitrogenous substances was essentially such as would be expected from the regimen used. It is particularly interesting to note that on November 18 and 19, while the subject was immobilized in bed following a fracture, the creatin excretion in the urine was markedly diminished. Eighteen days later, 5 days after resumption of usual activity, the creatin in the urine was still 2 to 3 times as great as that usually found in this subject.

While the preformed creatinin remained essentially constant, extreme variations occurred in the urine creatin. On one occasion an increase was probably due to extreme muscular activity. However, other variations from 48 to 190 mg. in 24 hours could not be accounted for on this basis.

With the expectation that variations in the food intake might account for some of the unexplained increase in creatin, an experiment was devised to study the creatin output while on a minimum nitrogen intake. Two normal male subjects were chosen (F. H. L. T. and W. B. C.). One who engaged in no great muscular activity and one who normally took considerable exercise and who carried on his usual activities during the experiment. After a preliminary control period of unrestricted hospital diet both subjects were placed on the same experimental diet. The diet provided approximately 2800 calories chiefly in the form of carbohydrate and fat, the protein being restricted to from 2 to 3 gm. a day. The fat was in the form of olive oil and butter. The protein was derived from an ounce of cream and a teaspoonful of potatoes daily. The chief source of carbohydrate was orange juice saturated with cane sugar. Fresh greens, vinegar, salt and so forth, were permitted as desired.

The urines were collected in the way described above. A partition of the urine nitrogen constituents was made (Table 4). It will be noticed that the preformed creatinin remained essentially the same, although the urea and total nitrogen fell to the minimum limits. During the last 4 days the urine creatin reached a constant figure in both subjects.

It is noteworthy that the urine creatinin in the second subject (W. B. C.) rose slightly during the restricted protein period. On February 11, 1934, this patient spent a day skiing. The low volume of urine on this day was due to excessive perspiration. An increase in creatin followed and was still present 2 days later.

In the case of the first subject there was a slight diminution of the creatin over the 15-day experimental period. In general in this experiment there seems to be a relative independence of the basal amount of creatin in the urine to the protein intake. It must be remembered, of course, that both of these subjects were receiving sufficient protein to protect the body proteins.

Discussion. It appears from the foregoing protocols that creatin may appear in the urine of normal adult males in detectable amounts. While it is true that in some cases the amount of creatin present is

TABLE 3.—SUBJECT T.

Age.	Sex.	Height, in.	Weight, lbs.	Diet.	Urine volume, ml.	Specific gravity.	Total nitrogen,* gm.	Preformed creatinin nitrogen,* gm.	Creatin nitrogen,* gm.	Date.	Remarks.
33	Male	68	126	Usual hospital diet	2200	1.015	13.56	0.580	0.015	11/18/33	Convalescent, in bed, from fracture of wrist.
					1550	1.017	13.00	0.554	0.027	11/19/33	
					2360	1.009	13.72	0.508	0.191	11/23/33	Restricted floor privileges.
										11/26/33	Discharged from hospital.
				Uncontrolled diet	2800	1.013	15.30	0.562	0.125	12/ 5/33	Usual activity.
					2240	1.015	14.95	0.504	. . .	12/ 7/33	Usual activity.
					2310	1.025	13.65	0.496	0.196	12/11/33	Usual activity.
				+10 gm. daily nucleic acid	3125	1.021	15.15	0.582	0.033	12/14/33	Usual activity.
					2250	1.021	12.20	0.485	0.047	12/19/33	Usual activity.
					3000	1.020	14.15	0.529	0.178	12/21/33	Violent exercise.
				+10 gm. daily hydrolyzed nucleic acid	1380	1.028	11.25	0.500	0.068	12/26/33	Usual activity.
					1750	1.026	10.67	0.511	0.091	12/28/33	Intermittent diarrhea from medication ingested.
					1450	1.025	9.68	0.488	0.053	1/ 4/34	

* All values in gm. per 24 hours.

TABLE 4.—CREATINURIA WITH MINIMUM NITROGEN INTAKE.

Subject.	Age.	Weight. lbs.	Height in.	Diet.	Date.	Volume, ml.	Specific gravity.	Uric acid nitrogen,* gm.	Urea nitrogen,* gm.	Preformed creatinin nitrogen,* gm.	Creatin nitrogen,* gm.	Ammonia nitrogen,* gm.	Amino acid nitrogen,* gm.	Total nitrogen,* gm.	Residual nitrogen,* gm.
F. H. L. T. .	33	126	68	Ordinary hospital house diet	12/14/33	3125	1.021	0.350	12.880	0.582	0.057	0.435	0.357	15.150	0.503
					12/26/33	1380	1.028	0.209	8.630	0.500	0.068	0.224	0.158	11.250	1.369
					1/28/34	1750	1.026	0.218	8.980	0.511	0.091	0.329	0.156	10.670	0.385
				Total calories, 3000. Protein restricted to 3 gm. daily	2/ 1/34	1450	1.025	0.168	8.230	0.408	0.053	0.232	0.092	9.680	0.497
					2/ 8/34	2310	1.008	0.212	2.730	0.455	0.031	0.423	0.090	5.590	1.649
					2/11/34	2410	1.006	0.197	2.040	0.579	0.091	0.274	0.126	5.210	1.903
					2/13/34	1620	1.012	0.161	1.440	0.480	0.032	0.265	0.064	3.620	1.078
					2/15/34	1340	1.017	0.170	0.820	0.522	0.038	0.352	0.032	3.860	1.926
W. B. C. . .	33	134	68	Ordinary hospital diet	12/14/33	2230	1.014	0.179	9.150	0.512	0.042	0.382	0.068	10.990	0.657
					12/26/33	1590	1.016	0.142	11.600	0.567	0.054	0.415	0.120	14.600	1.602
					1/28/34	1660	1.021	0.175	11.520	0.590	0.088	0.314	0.212	14.320	1.421
				Total calories, 3000. Protein restricted to 3 gm. daily	2/ 6/34	2230	1.012	0.222	3.310	0.573	0.047	0.060	0.074	4.210	0.000
					2/ 8/34	1870	1.014	...	2.320	...	...	...	...	5.160	...
					2/11/34	900	1.026	0.158	1.870	0.660	0.073	0.154	0.076	2.910	0.000†
					2/13/34	1560	1.013	0.188	1.770	0.563	0.182	0.212	0.072	3.970	0.983†
					2/15/34	2000	1.017	0.267	1.350	0.596	0.088	0.366	0.144	4.350	1.575
					2/18/34	1250	1.021	0.168	1.520	0.592	0.094	0.178	0.098	3.120	0.564

* Values as gm. per 24 hours.

† Exercise.

but 10% of the total creatinin, it will be observed that the difference is always positive, and two methods for determination have been used. The amount of creatin so found varies markedly from day to day. In many male patients under observation the creatin in the urine fluctuates from zero to 100 mg. per 24 hours. This finding may account for the fact that creatin determinations on a single 24-hour specimen may give negative results. In one individual whose urine has been analyzed at frequent intervals over the past 5 years creatin has been found in varying amounts. The latest data on this subject (Table 3) show amounts varying between 50 and 175 mg. in 24 hours, with only slight changes in the creatinin during normal activity. It is of some interest to note that this subject showed a much diminished creatin after confinement to bed for 10 days. The excretion of creatin was much increased after limited floor privileges were restored, and was still elevated 18 days later. This is not always the case, however, because many patients, both male and female, who have been hospitalized with complete bed rest for weeks do not always show progressive decrease of creatinuria, although they may show some increase after discharge. Patient W. (Table 2), however, showed such progressive decrease in creatin in the urine during the few days of complete bed rest.

Experimental work on children and dogs[6,7,8,9,10] has shown increases in the urinary creatin with increased protein intake. In an attempt to discover whether the creatinuria in the 2 adult male subjects studied was due to exogenous creatin, a restricted protein diet was used with the results given above. The two points of interest in the experiments were that both subjects maintained a creatinuria, although the total nitrogen output was reduced to minimum limits and that in 1 patient following exercise a somewhat elevated output was found. These data are confirmatory also of the endogenous nature of creatinin and creatin and to some extent indicate their relationship to health and muscular activity.[4,11,12]

Thus the data presented indicate that creatin occurs in small amounts in the urines of some adult males, either continuously or occasionally. There is some evidence confirmatory of the findings of Light and Warren[4] that at least some portion of the creatinuria may be due to changes in the degree of muscular activity or the performance of *unusual* muscular work. The amounts of creatin usually found are within the ranges found by these authors. The incidence of creatinuria in normal adult males was not determined as the series was too small. That it did occur in such a high percentage of the individuals studied may be chance. It should be pointed out, however, that the variations of creatin in the urine of a given individual are so marked that more than one determination should be made before reporting the complete absence of this substance.

Summary. 1. Creatin has been found in the urine of 15 adult males in amounts varying between 0 and 196 mg. of creatin nitrogen per 24 hours.

2. This amount of creatin was not materially changed by marked restriction of the protein intake.

3. Some data are presented suggesting that unusual muscular activity or sudden change in muscular activity may result in an increase of the creatin excreted.

REFERENCES.

1. Folin, O., and Dennis, W.: On Creatine in the Urine of Children, J. Biol. Chem., **11**, 253, 1912.

2. Rose, W. C.: Experimental Studies on Creatine and Creatinine. III. Excretion of Creatine in Infancy and Childhood, Ibid., **10**, 265, 1911–1912.

3. Harding, V. J., and Gaebler, O. H.: On the Constancy of the Creatine-Creatinine Excretion in Children on a High Protein Diet, Ibid., **54**, 579, 1922.

4. Light, A. B., and Warren, C. R.: Creatinuria Among Adolescent Males, Ibid., **104**, 121, 1934.

5. Folin, O.: Laboratory Manual of Biological Chemistry, 5th ed., New York, D. Appleton-Century Company, Inc., p. 163, 1934.

6. Talbot, F. B., and Gamble, J. L.: The Protein Metabolism of an Infant, Am. J. Dis. Child., **12**, 333, 1916.

7. Dennis, W., and Kramer, J. G.: The Influence of Protein Intake on Creatine Excretion in Children, J. Biol. Chem., **30**, 189, 1917.

8. Gamble, J. L., and Goldschmidt, S.: A Study of Creatinuria in Infants. II. Relation of Protein Intake to Urinary Creatine, Ibid., **40**, 215, 1919.

9. Harding, V. J., and Young, E. G.: The Exogenous and Endogenous Nature of the Creatinuria in the Growing Dog, Ibid. (Proc.), **41**, xxxv, 1920.

10. Harding, V. J., and Gaebler, O. H.: The Influence of the Positive Nitrogen Balance Upon Creatinuria During Growth, Ibid., **57**, 25, 1923.

11. Folin, O.: Laws Governing the Chemical Composition of Urine, Am. J. Physiol., **13**, 66, 1905.

12. Hodgson, P., and Lewis, H. B.: Physical Development and the Excretion of Creatine and Creatinine by Women, Ibid., **87**, 288, 1928.

THE FILTERABLE CALCIUM OF BLOOD SERUM.

I. A COMPARISON OF FILTERABLE CALCIUM OF SERUM AND TOTAL CALCIUM OF CEREBROSPINAL FLUID IN NORMAL, HYPERPARATHYROID, AND HYPOPARATHYROID STATES.

BY RAYMOND GREGORY, PH.D., M.D.,
INSTRUCTOR IN MEDICINE, STATE UNIVERSITY OF IOWA,
AND
MARIE ANDERSCH, PH.D.,
RESEARCH ASSISTANT IN MEDICINE, STATE UNIVERSITY OF IOWA, IOWA CITY.

(From the Department of Internal Medicine.)

RONA and Takahashi[1] showed that part of the serum calcium is diffusible and part non-diffusible. Numerous investigators [2–9] have confirmed and extended these observations, and, as a result, normal values for a number of species, including man, have been established.

Cameron and Moorhouse[10] suggested that spinal fluid calcium represents the filterable calcium of plasma. This theory was based on the assumption that the capillary wall and the endothelial membrane of the choroid plexus form a more nearly perfect semipermeable membrane than any artificial one. Merritt and Bauer[11,12] also supported this point of view, and Cantarow,[13,14,15] apparently satisfied that it is correct, has reported spinal fluid calcium values as filterable calcium of serum in a variety of pathologic conditions.

It is true that most comparative studies of serum and spinal fluid calcium have demonstrated that the filterable calcium of the former very closely approximates the total calcium of the latter, but in certain instances the differences have been too large to be accounted for by experimental error.[16]

Only 4 cases of hyperparathyroidism in which observations on the filterable calcium had been made could be found in the literature. Snell[17] reported one determination of the total and filterable serum calcium in a case of hyperparathyroidism. The filterable calcium percentage of the total was within normal limits, and the amount of filterable calcium (6.1 mg. %) was less than that in one of the controls (6.3 mg.%). Benjamin and Hess,[18] who introduced the concept that the serum calcium exists in four fractions, two diffusible and two non-diffusible, reported studies on one case of hyperparathyroidism. The sum of their "filterable" and "ionized" fractions, which is equivalent to the diffusible or filterable fractions of other authors, was found to be increased. Herbert[19] has studied the total and diffusible serum calcium in 2 cases of undoubted hyperparathyroidism. Her studies of diffusible serum calcium were made at long intervals, and in each case there was but one comparison of the cerebrospinal fluid calcium and the diffusible serum calcium. In both cases there was an increase in the filterable serum calcium, and the spinal fluid calcium, although slightly elevated, was significantly less than the filterable serum calcium. Two determinations of the spinal fluid calcium on the same patient, made at an interval of 6 weeks, both of which gave the same result, suggests that time is not the factor responsible for the difference between the values for diffusible serum calcium and spinal fluid calcium. Herbert's 2 cases of osteitis fibrosa, in which the serum calcium and inorganic phosphorus values were normal, do not conform to the commonly accepted diagnostic criteria of hyperparathyroidism.

Very few comparative studies of the spinal fluid calcium and filterable serum calcium in cases of hyperparathyroidism and hypoparathyroidism have been reported, and in only 1 case of hyperparathyroidism (Herbert) have repeated determinations been made. For these reasons, daily simultaneous determinations of total and filterable serum calcium and spinal fluid calcium were made in 2 cases of hyperparathyroidism and 2 of hypoparathyroidism in the endeavor to ascertain whether there was any variation in the spinal fluid calcium and filterable serum calcium over a period of weeks.

In all previous studies of the spinal fluid calcium, particularly those dealing with comparisons between filterable serum calcium and total spinal fluid calcium, the authors have apparently assumed that the spinal fluid calcium is completely filterable. We have considered it desirable to test this assumption experimentally.

Material. Patients on the Neurologic Service who were free from organic disease of the central nervous system which might affect the permeability of the membranes of the chorioid plexus (*i. e.*, as attested by normal spinal fluid under normal pressure) were used as controls.

Characteristic generalized roentgenographic changes in the bones, high serum calcium, low serum inorganic phosphorus, high serum phosphatase and hypercalcinuria were the diagnostic criteria of hyperparathyroidism. Additional proof of the correctness of the diagnosis in 1 case (G. J.) was afforded by the abrupt fall in serum calcium following removal of a parathyroid adenoma.*

The validity of the commonly accepted criteria of hyperparathyroidism (hypercalcemia, hypercalcinuria, hypophosphatemia) has recently been questioned by Robbins and Kydd,[20] who state that they have found similar abnormal phosphorus and calcium values in 3 cases of multiple myeloma and 1 case of Paget's disease (osteitis deformans). Previously Bauer[21] and Compere[22] had been unable to demonstrate these changes in Paget's disease. In our work we have adhered to the diagnostic criteria accepted by most investigators.[21,22,23]

A history of convulsions following thyroidectomy, strongly positive Chvostek's and Trousseau's signs, low serum calcium, and high inorganic phosphorus served as the basis for the diagnosis of hypoparathyroidism in 1 of our cases (O. C.). The appearance after thyroidectomy of mild tetany, a feeling of numbness in the upper extremities, inability to relax, a positive Chvostek's sign, and low serum calcium established the diagnosis in the second case of hypoparathyroidism (C. E.).

In 1 case (O. C.) a single determination was made at the end of a 6 months' period of calcium and parathyroid extract administration; treatment was then discontinued, and thereafter repeated determinations were made until tetany supervened and after specific treatment had been resumed. In the other case (C. E.) the estimations were made 3 months after thyroidectomy, during which time no treatment had been administered, and again after the institution of treatment with calcium and parathyroid extract.

Methods and Experimental Procedure. Approximately 25 cc. of blood were removed from a vein in the usual manner. Venipunctures were done without regard to meals except when inorganic phosphorus was to be estimated, in which case the sample was taken after a fast of 12 to 14 hours.

* Since this article was submitted for publication, the diagnosis of hyperparathyroidism has been proved in the case of E. W., by the removal of a parathyroid adenoma, with the resulting rapid return to normal of the blood calcium and phosphorus values.

Cerebrospinal fluid was obtained either by lumbar or cisternal puncture not more than 5 minutes before the venipuncture.

Clark and Collip's[24] modification of Tisdall's[25] method was used for all calcium determinations. Inorganic phosphorus was estimated by the method of Fiske and Subbarow.[26] The method of Andersch and Gibson[27] was used for total protein. All determinations were done in duplicate except when accident prevented. Eighty-five per cent of the duplicates of the filterable calcium checked within 5%, and the remainder checked within 10%. The calcium of the ultrafiltrate was recalculated according to the formula given by Benjamin and Hess[18] to correct for the quantity of protein in the serum.

Collodion sacs were prepared from Mallinckrodt's parlodion by Greenberg and Gunther's[4] method. To avoid the possibility of error due to passage of protein into the filtrate, all filtrates which gave a positive biuret test were discarded. The permeability of the membranes to calcium chlorid solutions was tested frequently and always found to be complete. The close agreement between calcium values of ultrafiltrates obtained from the

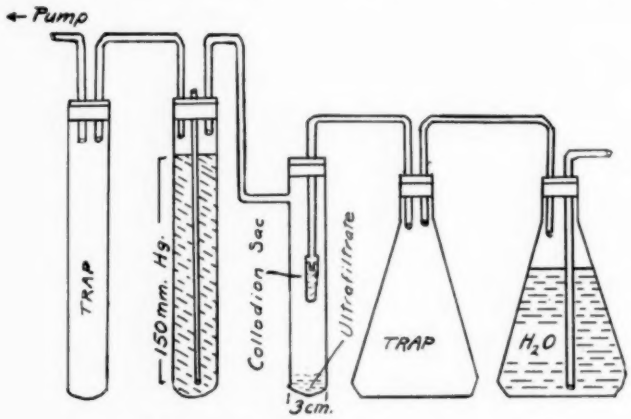

FIG. 1.—Schematic drawing of ultrafiltration apparatus.

same serum by filtering through different membranes also served as a check on the permeability of the membranes. All sacs were discarded after being used once. An ultrafiltrate of the serum was obtained by the method of Greenberg and Gunther,[4] which is essentially the one described by Updegraph, Greenberg, and Clark.[8] Several minor modifications were made to simplify the apparatus and to insure more rapid filtration (Fig. 1). If 7 to 8 cc. of serum be used in each sac, 2 cc. of filtrate are obtained in 2 hours.

Results. Tables 1, 2, and 3 summarize our results for total serum calcium, filterable serum calcium, and spinal fluid calcium in a group of normal individuals, in 2 cases of hyperparathyroidism, and 2 cases of hypoparathyroidism, respectively.

Discussion. It may be seen from Table 1 that the values for filterable calcium of blood serum are within the normal limits reported by others.[5,8,18,19] Furthermore, the results indicate that over the normal range of serum calcium values the filterable calcium of the serum and the calcium of the spinal fluid are approximately

the same, as Searle and Michaels[28] have shown. In 2 normal subjects (L. and R., Table 1), however, the difference between the filterable calcium of the serum and the calcium of the spinal fluid

TABLE 1.—CALCIUM STUDIES IN A GROUP OF NORMALS.
(ALL CALCIUM VALUES IN MG. %.)

Patient.	Date.	Serum calcium. Total.	Serum calcium. Filterable.	Spinal fluid calcium. Total.	Spinal fluid calcium. Filterable.	Serum protein, %.
H	12- 7	10.4	5.2	...	...	6.2
F	12- 8	10.6	4.3	4.7	4.8	5.0
W	12-13	11.0	4.9	5.3	5.1	7.4
L	12-13	10.1	5.3	4.7	4.6	7.3
M	12-13	11.3	3.3	...	...	6.0
M	12-15	11.4	3.5			
M	12-19	10.0	4.2			
C	12-20	10.4	4.8	4.9	...	5.8
H	12-20	10.4	5.6	5.5	...	6.3
R	1- 4	10.2	5.3	4.4	...	5.2
T. R.	1- 4	9.2	5.5	4.8	...	5.6

TABLE 2.—CALCIUM STUDIES IN 2 CASES OF HYPERPARATHYROIDISM.
(ALL CALCIUM VALUES IN MG. %.)

Patient.	Date.	Serum calcium. Total.	Serum calcium. Filterable.	Spinal fluid calcium. Total.	Spinal fluid calcium. Filterable.	Serum protein, %.
E. W.	11-22	15.3				
	12- 8	16.5				
	12-10	16.2	6.9	5.8	...	7.0
	12-12	15.4	...	...	...	7.7
	12-13	15.3	5.8	6.0	6.1	6.9
	12-14	15.7	7.3	...	...	7.4
	12-15	15.0	7.1	...	...	7.0
	12-17	16.2	7.8			
	12-18	16.5	7.3	5.6		
	12-19	14.9	6.5	...	...	7.0
	12-20	15.4	6.8	5.9	6.0	7.2
	12-21	14.1	6.9	6.4	6.3	6.9
	12-31	16.3	7.1	5.5		
	1- 2	14.3	8.0			
	1- 3	15.2	8.1			
	1- 5	15.0	7.8	...	...	7.0
	1-25	15.6	8.7			
Average	...	15.3	7.2	5.8		
G. J.	12-31	12.3	7.3	4.4	4.6	5.2
	1- 1	12.7	7.1	...	...	5.2
	1- 2	12.7	6.9	...	...	5.4
	1- 3	12.9	7.5	...	...	5.4
	1- 4	13.1	7.7	5.0	5.2	
	1- 5	14.6	7.6	...	...	5.4
	1- 7	12.3	7.0	4.8		
Average	...	13.0	7.3	4.8		
	2-20*					
	2-20†	11.8				
	2-21	10.2				
	2-22	8.4				
	2-23	7.4	3.4			
	3- 1	7.3	3.4			
	3- 6	7.2	3.4			
	3-11	7.2	3.6			
	3-12	6.7	2.8	4.7		

* 8 A.M. Removal of proven parathyroid adenoma.
† 4 P.M.

TABLE 3.—CALCIUM STUDIES IN 2 CASES OF HYPOPARATHYROIDISM. (ALL CALCIUM VALUES IN MG. %.)

Patient.	Date.	Serum calcium.		Spinal fluid calcium, total.	Serum protein, %.	Remarks.
		Total.	Filterable.			
O. C.	1–15	7.6	3.4	...	5.6	After 6 mos. on calcium and parathyroid extr., which was discontinued on this date.
	1–17	6.1	2.3	3.7	5.6	
	1–18	6.5	2.4			
	1–19	6.3	2.3	4.8	5.6	
	1–21	6.1	2.4			
	1–22	5.6	1.9	4.2	5.4	Tetany; 4 cc. parathyroid extr. and 5 gm. calcium lactate daily started and continued to 2–5.
	1–23	6.2	2.3	...	5.4	
	1–25	6.7	2.9	4.3	5.6	
	1–28	8.2				
	1–31	7.6	3.5	...	5.2	
	2– 5	7.4	3.0	...	5.2	
C. E.	3– 4	6.1				
	3– 6	5.8	2.5	...	5.6	
	3– 7	6.1	2.3	4.1	5.6	
	3–11	5.4	2.3	3.9		
	3–15	...	...	...	...	5 gm. calcium lactate and 1 cc. parathyroid extr. daily started.
	3–20	7.0	4.7			
	3–21	7.0	4.2			
	3–25	7.8	4.2			
	4– 3	7.5				
	4– 6	...	...	...	...	Parathyroid extr. 3 cc. daily.
	4– 3	7.5				
	4–11	9.9				
	4–22	9.2	5.5	3.9		

is greater than the experimental error. The cerebrospinal fluid values, which varied between 4.4 to 5.5 mg.%, are in close agreement with the normal spinal fluid calcium values of 4.5 to 5.5 mg.% reported by Cantarow[13] and Searle and Michaels.[28]

In 1 case of hyperparathyroidism (E. W.), in which the total calcium averaged 15.3 mg.%, the filterable calcium of the serum averaged 7.2 mg.% (range 5.8 to 8.7 mg.%) over a period of 2 months, which is definitely higher than normal. Six estimations of spinal fluid calcium varied from 5.5 to 6.4 mg.%, averaging 5.8 mg.%, which, although very slightly elevated, is considerably lower than the average (7.2 mg.) for filterable calcium of serum in this case.

In the second case of hyperparathyroidism (G. J.), in which the total serum calcium averaged 13.0, the filterable calcium averaged 7.3 mg.%. The spinal fluid, however, was consistently within normal limits, varying between 4.4 and 5 mg.%. The results in these 2 cases of hyperparathyroidism are in agreement with those

obtained by Merritt and Bauer[11] after administering parathyroid extract to normal human beings, and with the results in 2 cases of hyperparathyroidism reported by Herbert.[19]

Since all our observations were made over a considerable period of time, it follows that the lack of correlation between filterable serum calcium and cerebrospinal fluid calcium is not due to failure of the cerebrospinal fluid calcium to reach an equilibrium with the calcium of the blood serum, as has been suggested by Greenberg.[29]

It should be noted also that the correct relationship between cerebrospinal fluid calcium and filterable serum calcium cannot be arrived at if only single comparisons are made, since there are independent fluctuations in the two. For example, in the case of E. W. there was perfect agreement on one day (5.8 and 6), and considerable disparity on another (7.3 and 5.6).

In his contention that ankylosing (rheumatoid) polyarthritis may be due to hyperparathyroidism, Funsten[30] has not demanded permanent elevation of the serum calcium as a necessary criterion of hyperparathyroidism. The serum calcium in our 2 cases of hyperparathyroidism was invariably elevated. This is in agreement with the results of other investigators.[21,23]

After taking 1 cc. of parathyroid extract and 60 grains of calcium lactate daily for several months, 1 patient (O. C.) with hypoparathyroidism had a total serum calcium of 7.6 mg.% and a filterable calcium of 3.4 mg.%. After the parathyroid extract and calcium were discontinued there was a progressive fall of both the total and filterable calcium values. On the sixth day the total serum calcium reached 5.6 mg.% and the filterable calcium 1.9 mg.%, and the patient showed definite signs of tetany (spontaneous carpopedal spasm). In contrast to this fall in the filterable calcium of serum, the cerebrospinal fluid calcium rose slightly from 3.7 to 4.8 mg.%. At this point the daily administration of 4 cc. of parathyroid extract subcutaneously and 60 grains of calcium lactate orally was begun. The total and filterable calcium rose progressively, but the latter never reached the level of the spinal fluid calcium. After 2 weeks of this therapy the total serum calcium was only 7.4 mg.% and the filterable calcium was 3 mg.%.

In the second case of hypoparathyroidism (C. E.) the total and filterable calcium were much diminished, whereas the spinal fluid calcium was essentially normal. Parathyroid and calcium therapy caused the total serum calcium to rise essentially to a normal level and the filterable calcium to return to a high normal value. The spinal fluid calcium however, remained unchanged. At the beginning of the study, the spinal fluid calcium was 3.9 mg., the total calcium 5.4 mg., and the filterable calcium 2.3 mg. With therapy the total rose to 9.2 mg., the filterable rose to 5.5 mg., and the spinal fluid calcium remained at 3.9 mg.

The results in these cases (O. C. and C. E.) indicate that it is

principally the filterable calcium of the serum which falls in parathyroid tetany. This agrees with the results of Gunther and Greenberg.[5] It is not in agreement, however, with the observations of Cameron and Moorhouse,[10] who reported that the non-filterable calcium of serum almost disappeared in parathyroid tetany in dogs. The last named investigators used the spinal fluid calcium as a measure of the filterable calcium of serum.

Summary. Estimations of the total and filterable calcium of serum and the total calcium of the spinal fluid were made in 9 persons with normal calcium metabolism. A series of comparisons of the total and filterable calcium of serum with the total spinal fluid calcium was made in 2 cases of hyperparathyroidism and 2 cases of hypoparathyroidism. In each person with abnormal calcium metabolism the comparisons were repeated frequently at intervals of one to several days over an extended period of time. This was done in order to ascertain whether there might be daily variations in the relationship of the serum filterable calcium and spinal fluid calcium, and to be sure that any discrepancy between the two values was not due to failure of the two systems to reach equilibrium because of a time factor. The filterability of the spinal fluid calcium was also studied in subjects with normal and abnormal calcium metabolism.

Conclusions. 1. Filterable calcium of serum is elevated in hyperparathyroidism and lowered in hypoparathyroidism.

2. Filterable calcium of serum and total calcium of spinal fluid are usually practically equal over the normal range of serum calcium values. In 2 of 9 persons in our normal series, however, the filterable calcium of serum exceeded the total spinal fluid calcium by an amount greater than the usual experimental error.

3. The spinal fluid calcium was slightly elevated in 1 case of hyperparathyroidism and normal in another case. It was also normal in 2 cases of hypoparathyroidism.

4. Wide variations in filterable calcium of serum may occur without any change in the spinal fluid calcium. It is proper, therefore, to question all values for filterable serum calcium which are obtained by estimating the spinal fluid calcium.

5. The calcium of spinal fluid is completely filterable.

6. It was impossible to raise the total serum calcium above 7.6 mg. in 1 case of hypoparathyroidism by administering 4 cc. of parathyroid extract and 4 gm. of calcium lactate daily, but the symptoms and signs of tetany were completely relieved.

7. In 1 proved case of hyperparathyroidism, the maximal change in the serum calcium values occurred within 3 days after the removal of the parathyroid adenoma. This should be kept in mind in using the serum calcium as the criterion of success of surgical treatment of parathyroid adenomas.

8. Time was not the determining factor in the difference between the filterable serum and spinal fluid calcium in 4 patients with abnormal calcium metabolism.

9. The spinal fluid probably does not represent an ultrafiltrate of the plasma so far as calcium is concerned.

BIBLIOGRAPHY.

1. Rona, P., and Takahashi, D.: Biochem. Zeit., **31**, 336, 1911.
2. Loeb, R. F.: J. Gen. Physiol., **6**, 453, 1924.
3. Neuhausen, B. S., and Pincus, J. B.: J. Biol. Chem., **57**, 99, 1923.
4. Greenberg, D. M., and Gunther, L.: Ibid., **85**, 491, 1930.
5. Gunther, L., and Greenberg, D. M.: Arch. Int. Med., **47**, 660, 1931.
6. Gunther, L., and Greenberg, D. M.: Ibid., **45**, 983, 1930.
7. Nicholas, H. O.: J. Biol. Chem., **97**, 457, 1932.
8. Updegraph, H., Greenberg, D. M., and Clark, G. W.: Ibid., **71**, 87, 1926.
9. Cushny, A. R.: J. Physiol., **53**, 391, 1920.
10. Cameron, A. T., and Moorhouse, V. H. K.: J. Biol. Chem., **63**, 687, 1925.
11. Merritt, H. H., and Bauer, W.: Ibid., **90**, 233, 1931.
12. Merritt, H. H., and Bauer, W.: Ibid., p. 215.
13. Cantarow, A.: Arch. Int. Med., **44**, 667, 1929.
14. Cantarow, A.: Ibid., p. 670.
15. Cantarow, A.: Am. J. Med. Sci., **179**, 497, 1930.
16. McCance, R. A., and Watchorn, E.: Quart. J. Med., **24**, 371, 1931.
17. Snell, A. M.: Proc. Staff Meet. Mayo Clin., **5**, 17, 1930.
18. Benjamin, H. R., and Hess, A. F.: J. Biol. Chem., **100**, 27, 1933.
19. Herbert, F. K.: Biochem. J., **27**, 1978, 1933.
20. Robbins, C. L., and Kydd, D. M.: J. Clin. Invest., **14**, 220, 1935.
21. Bauer, W.: J. Bone and Joint Surg., **15**, 135, 1933.
22. Compere, E. L.: Ibid., p. 142.
23. Albright, F., Aub, J. C., and Bauer, W.: J. Am. Med. Assn., **102**, 1276, 1934.
24. Clark, E. P., and Collip, J. B.: J. Biol. Chem., **63**, 461, 1925.
25. Tisdall, F. F.: Ibid., **56**, 439, 1923.
26. Fiske, C. H., and Subbarow, Y.: Ibid., **66**, 375, 1925.
27. Andersch, M., and Gibson, R. B.: J. Lab. and Clin. Med., **18**, 816, 1933.
28. Searle, O. M., and Michaels, J. J.: Am. J. Physiol., **103**, 455, 1933.
29. Greenberg, D. M.: Proc. Soc. Exp. Biol. and Med., **27**, 514, 1930.
30. Funsten, R. V.: J. Bone and Joint Surg., **15**, 112, 1933.

CAUSES OF DEATH IN DIPHTHERIA AND THEIR PREVENTION.*

By Archibald L. Hoyne, M.D.,

MEDICAL SUPERINTENDENT, MUNICIPAL CONTAGIOUS DISEASE HOSPITAL; ATTENDING PHYSICIAN AND CHIEF, DEPARTMENT OF CONTAGIOUS DISEASES, COOK COUNTY HOSPITAL, CHICAGO, ILL.

(From Municipal Contagious Disease Hospital, Chicago Board of Health.)

One might properly suggest that the simplest manner for preventing deaths from diphtheria is through active immunization. We not merely agree that this is quite true but are willing to admit that it is the only certain method of eliminating fatalities from this infection. Nevertheless, just as smallpox has continued to exist

* Read before the Chicago Society of Internal Medicine, May 27, 1935.

and cause an unnecessary loss of life for the 139 years since the introduction of vaccination, so a somewhat similar situation may be expected in respect to diphtheria. Many parents will fail to protect their children by the means now available. It is among this portion of the population who contract diphtheria with which we are now concerned.

The causes of death from diphtheria fall into three classes: (1) asphyxia; (2) bronchopneumonia, and (3) myocarditis (toxemia).

The first group embraces those cases of diphtheria in which the membrane is located within or below the larynx. And a false membrane within or below the larynx does not necessarily signify an extension of the infection from above downward, for in the majority of laryngeal diphtheria patients there is no visible membrane outside the larynx. In reality, many cases of this kind develop by extension of the diphtheritic process from below upward. This fact has an important bearing on the treatment required.

In the average case of diphtheria, when the site of the membrane is in or below the larynx, toxemia is not the primary factor that endangers life. It is the membrane itself acting in a mechanical way that threatens asphyxiation by blocking the lower air passages. Consequently relief from this condition must be accomplished either by intubation or tracheotomy. Diphtheria antitoxin alone, regardless of dosage, will seldom suffice to save the patient. We have stated that usually the toxic action of diphtheritic infections in this group is not pronounced. As evidence of this, it is found that the complications associated with other forms of diphtheria rarely occur when the infection (membrane) is confined to the larynx or trachea. Myocarditis, albuminuria and the paralyses are notably absent.

Asphyxiation, then, as a cause of death in diphtheria must be prevented by surgical, not medical, treatment. Here diphtheria antitoxin is not the artillery: it is the infantry in the fight for life.

In the second class of causes of death from diphtheria, we must contend with bronchopneumonia. This is perhaps the most difficult onslaught to avoid, because there is no certain method of prevention. Nor is there any reasonably sure means of victory after bronchopneumonia is firmly entrenched. It is principally in laryngeal diphtheria that bronchopneumonia may intervene and snuff out a life after intubation or tracheotomy has saved the patient from asphyxiation. Aspiration pneumonia in intubated patients is not nearly as frequent as some would have us believe. It is always a possibility, nevertheless. With proper methods of feeding, however, it is not likely to occur. Clean hands and clean instruments when performing an intubation are vital necessities. With these simple requirements we found some years ago that the frequency of bronchopneumonia as a cause of death in diphtheria could be greatly diminished. The use of mechanical suction appa-

ratus and elevating the foot of the bed are also important assets in the avoidance of pneumonia in those patients who have profuse nasal or oral discharges.

In the third class of the causes of death in diphtheria we have the most important group. It holds this position not merely because it constitutes the greatest number of fatalities, but also on account of the possibilities of prevention, providing the signs of impending disaster are promptly recognized and immediate and appropriate action taken.

This is the group in which myocarditis so often plays the part of the executioner. However, the death sentence is not carried out with any undue haste. The limitation of life cannot be compared with the patient who suffers from laryngeal diphtheria when, within the space of a few seconds the possession of dexterity and experience, or lack of it, on the part of the physician, determines the outcome.

In pharyngeal or nasopharyngeal diphtheria, the absorption of toxin from the site of the membrane is rapid. Within 3 days of the onset of the disease, pronounced toxemia may be evident. Nevertheless, if treated with adequate doses of antitoxin within that period of time, comparatively few patients are lost. But when more than 3 days have elapsed prior to antitoxin treatment, the fatality figures mount by leaps and bounds, provided antitoxin alone is relied upon to preserve life. It is to such patients as these that we have directed particular attention during the past 2 years.

Diphtheria patients with a profound toxemia usually have a cervical adenitis, commonly described as the "bull neck type." The neck, however, does not have the hard brawny feeling that is sometimes encountered in scarlet fever. The tissues suggest that much of the swelling is due to edema. The patient is often not merely rational but very clear mentally. A profuse nasal discharge is likely, and a foul odor, sometimes referred to as typical of diphtheria, permeates the atmosphere about the patient. The finding of a marked albuminuria is very significant, for it indicates a bad prognosis. An enlarged and tender liver will also be noted in many such patients. The temperature means little, insofar as having any bearing on the true condition of the patient. It may be normal, slightly subnormal, or be elevated 3 to 4°. As a rule, the temperature ranges from 99 to 103° prior to antitoxin administration.

When one observes a patient such as described here, it is possible to foretell with a surprising degree of accuracy what may be expected and the approximate time when certain expectations will be fulfilled. After the administration of diphtheria antitoxin, the temperature will usually rise 2 or 3° during the next 12 to 24 hours. Within 48 hours after antitoxin injection, considerable improvement is often manifest and there are likely to be high hopes for recovery. During the next 2 or 3 days the membrane may have completely

disappeared and the pulse rate, which perhaps was 110 before antitoxin treatment, is now about 90. At this time, little or no abnormalities of the heart may be detected with the stethoscope, even in the hands of the heart specialist. However, from the 10th to the 12th day of the disease, which may be possibly 6 or 8 days after antitoxin has been given, a sharp drop in the pulse rate occurs. There is often a decline of 30 to 40 beats per minute within a space of a few hours. This is one of the commonest omens of impending danger, though the patient may have no complaint of ill feeling. However, within the next 12 to 24 hours, abdominal pain may occur, and if this is accompanied by vomiting, death is practically certain, and an autopsy establishes a diagnosis of acute myocarditis.

For a considerable number of years we have made such observations of diphtheria patients in the contagious disease hospitals. We have seen patients enter and found that we frequently could anticipate certain complications, basing our predictions on signs and symptoms present at that time. This has been particularly true in respect to myocarditis. When myocarditis did develop, we then made use of dextrose intravenously and this form of treatment seemed to be beneficial.

About a year ago,[1] we reviewed 496 cases of diphtheritic myocarditis, and undertook to emphasize the value of dextrose intravenously in the treatment of such cases. Our customary practice had been similar to that of others[2] who had used glucose intravenously in the treatment of diphtheritic myocarditis. We began the administration of glucose as soon as myocarditis was diagnosed. Yet in many instances we felt we knew several days in advance that the patients would have myocarditis. When the administration of glucose was withheld until a definite diagnosis of myocarditis was made, comparatively few such patients survived. Therefore, early in 1934, it was decided that certain classes of diphtheria patients would be placed on glucose therapy as soon as admitted to hospital, and a definite plan was adopted for both the Municipal Contagious and Cook County Contagious Disease Hospitals. Intravenous glucose was ordered as routine treatment for all diphtheria patients coming within any of the following groups: (1) those ill more than 3 days prior to receiving antitoxin; (2) "bull neck" types, irrespective of the day in the course of the disease that antitoxin was injected; (3) patients with marked albuminuria; (4) all postnasal cases and all malignant types of any character.

Patients classified according to any of the foregoing groups were placed on the critical list when admitted to the hospital. Glucose—10% in double distilled water—was administered at once by the gravity method. The quantity usually varied from 500 cc. for a child, to 1000 cc. for an adult, but was also determined to some extent by the condition of the patient. This treatment was repeated daily for a minimum period of 8 days, which frequently carried the

patient through the precarious stage (10th to 12th day of disease) during which diphtheritic myocarditis so frequently manifests itself.

In one instance, a woman, aged 39, receiving daily treatments was given 13,365 cc. of 10% glucose solution, or 1365 gm. of glucose, within 37 days.

Among 225 diphtheria patients admitted to the Municipal Contagious Disease Hospital in 1934, there were 83 classified as critical when they entered. Nearly all of these 83 were of a type usually described as malignant. However, we believed the severity of their infections in most instances should be attributed to delay in antitoxin administration rather than to some extreme virulence of the diphtheria bacillus. Many of these patients had been ill from 5 to 7 days before coming to the hospital. For the entire group of critical cases, the average duration of illness prior to antitoxin administration was 4.85. Hottinger[3] reported a fatality rate for malignant diphtheria in Düsseldorf of from 50 to 60%.

In our group of 83 critical diphtheria patients, the average number of days for glucose administration was 9, and the average total dose of 10% glucose solution, 3492 cc. Among these 83 patients there were but 10 deaths. Thus, the fatality rate was only 12% in contrast to a rate of from 30 to 60%, which would ordinarily be expected without glucose. Moreover, it seems worthy of mention that of the 10 deaths, 1 occurred in less than 1 hour after admission to the hospital, and another of the fatalities took place in less than 24 hours after admission. With the exclusion of these 2 deaths, we find that 81 so-called malignant cases of diphtheria that were placed on glucose therapy, had a recovery rate of more than 90%. Or in other words, the fatality rate was 9.8%, a figure that might not be regarded with disfavor for the average hospital cases of diphtheria. Nevertheless, the 83 patients treated with glucose were in desperate condition. In this connection it is rather interesting to find that the average dose of diphtheria antitoxin for the patients in this group was only 39,500 units. This fact, together with the successful results of treatment, seem to further justify our conclusions reached some years ago that massive doses of diphtheria antitoxin are neither necessary nor of value in saving lives when there has been unusual delay in serum administration.

Very recently, Darrow and Yannet[4] reported on the use of glucose in malignant diphtheria. In a group of 5 cases they had 4 recoveries and 1 death. These authors point out that diphtheritic intoxication produces extensive derangement of carbohydrate metabolism, and they further state there is hepatic insufficiency, renal insufficiency and shock. In reporting their clinical experience, it seems to me, however, that the mode of treatment adopted was much the same as used by others in the past. Glucose was given the patient in order to combat degenerative changes in the tissues after symptoms of such changes had become plainly evident. To be of most value,

glucose should be administered without waiting for physical signs of myocarditis.

Summary. 1. When the diphtheria membrane is located within or below the larynx, diphtheria antitoxin alone will seldom save the patient. Usually intubation or tracheotomy is required.

2. Although there is no absolute method for preventing bronchopneumonia in diphtheria, the frequency of this complication can be held to a minimum if minute attention is paid to cleanliness of hands and instruments when performing intubations, and if correct methods of feeding are followed for patients wearing intubation tubes.

3. Diphtheritic myocarditis can often be prevented by the use of 10% dextrose solution intravenously, provided this treatment is begun sufficiently early and continued daily for a sufficient length of time.

Dextrose helps to maintain the general nutrition of the patient who may be unable to swallow or retain food. In addition, it seems to provide nourishment to the heart muscle, and thus lessen passive congestion of the liver. The necessity for immediate institution of glucose therapy increases according to the number of elapsed days prior to antitoxin injection.

REFERENCES.

1. Hoyne, A. L., and Welford, N. T.: Diphtheritic Myocarditis, J. Pediat., **5**, 642, 1934.

2. Toomey, J. A.: Am. J. Dis. Child., **25**, 722, 1928.

3. Hottinger, A.: Ueber die maligne, sogenannte toxische Diphtherie, Berlin, S. Karger, 1932.

4. Darrow, D. C., and Yannet, H.: Symptomatic Therapy in Malignant Diphtheria, J. Dis. Child., **49**, 60, 1935.

BOOK REVIEWS AND NOTICES

DISEASES OF THE NERVOUS SYSTEM. A Text-book of Neurology and Psychiatry. By SMITH ELY JELLIFFE, M.D., PH.D., Formerly Professor of Psychiatry, Fordham University, and Adjunct Professor of Diseases of the Mind and Nervous System, New York Post-Graduate Medical School and Hospital, and WILLIAM A. WHITE, M.D., Superintendent of St. Elizabeth's Hospital, Washington, D. C.; Professor of Psychiatry, George Washington University, etc. Pp. 1175; 497 illustrations and 13 plates. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $9.50.

"IN the preparation of this edition the authors have undertaken to include as far as possible all important contributions which have sufficient weight and have been made since the last edition. The whole book has been carefully revised, some portions rewritten and many additions have been made to the text. That it has kept within the same number of pages as the last edition is due to the fact that the pages throughout have been enlarged so that the bulk of the book might not be increased materially. To be somewhat specific as to the nature of the new material, briefly it may be said that new methods of examination have been added; the chapter on the vegetative nervous system brought into line with present-day investigations, particularly the pathways of the hypothalamic region presented in the light of recent metabolic studies; the newer surgery of the sympathetics has been discussed and reserved judgments expressed. The endocrinopathies, especially the pituitary sections, have been rewritten. In the sensorimotor neurology, especially of the peripheral systems, little of signal importance has been produced since the last edition. The newer work on spinal cord lesions, especially the encephalomyelitides, has been carefully revised. Rarer peduncular and mid-brain lesions have been included and likewise certain new issues in the discussion of the localization of brain tumors. In the final section, on the symbolic systems, much new material has been added, particularly of an interpretative character, and especially material which tends to illustrate the distinction between those common possessions of man which have been laid down in well defined structuralizations and those more or less incidental results of his individual experiences during his lifetime. Especial attention is called to our effort in the full citation of the significant literature to indicate the historical developments in the knowledge of the various matters discussed." (From the Authors' Preface.)

THE PATHOLOGY OF INTERNAL DISEASES. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.); Dipl. Psych., F.R.S. (CAN.), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 904; 335 illustrations. Second edition. Philadelphia: Lea & Febiger, 1935. Price, $10.00.

THE first edition of Professor Boyd's book was reviewed in this Journal (**181**, 419, 1931). In this revised edition much of the book has been rewritten and a considerable amount of new material has been added. Every chapter bears witness to the successful accomplishment of the aim stated "to develop the subject along clinical and physiological lines." Stress has

been laid on relating structural changes to functional disturbances, symptoms to lesions. The introduction of a number of pictures of clinical conditions serves to emphasize this viewpoint. From the opening sentence ("Of all the ailments which may blow out life's little candle, heart disease is the chief") to the last page, the book is well written; it is also very readable, and not the least so because of the many apt quotations, some but a phrase or a line, from the original descriptions of lesions and symptoms by the masters.

As the title states, the book deals with the pathology of internal diseases, including those of the nervous system. The student in his preclinical as well as in the clinical years will find it an excellent aid for linking the pathologic laboratory to the ward; to the practitioner it will bring a thoroughly satisfactory and modern presentation of the science of internal diseases. B. L.

A Textbook of General Bacteriology. By Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Pp. 825; 202 illustrations. Eleventh edition, entirely reset. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

"The current—one might say torrent—of investigation has run strong since the tenth edition of this book was printed, and signal advances have been made in our knowledge. It has been necessary to rewrite many portions and to add materially to others. The important topic of bacterial variation is dealt with in a new and separate chapter; the chapters on Immunity, on Streptococci, on Salmonella, on Brucella, on Rickettsia and on Spirochetes have received many modifications and additions; and the section on The Viruses and Virus Diseases has been largely rewritten. In an attempt to promote grouping by natural relationships a few changes have been made in the arrangement of chapters. The most important of these has been to bring together the Actinomycetales: The diphtheria bacillus, the tubercle bacillus, the actinomyces, etc.

The problem of nomenclature, always in bacteriology a vexed and difficult one for both student and teacher, is treated in what some bacteriologists will consider too conservative a manner. The names for bacteria, however, used by many recent writers, notably by the authors of the admirable nine-volume System of Bacteriology published by the British Medical Research Council, is additional evidence of the impossibility of achieving a unified nomenclature except by international agreement. For the present we may well hesitate to use in a textbook names that have not won pretty general acceptance." (From the Author's Preface.)

A Textbook of Laboratory Diagnosis. With Clinical Applications for Practitioners and Students. By Edwin E. Osgood, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, Portland. Pp. 585; 27 illustrations and 10 colored plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $6.00.

"Among the major additions from the work of other investigators are the technic and interpretation of the blood urea clearance test, insulin coefficient, the blood bromide determination, the Friedman test, the galactose tolerance test, the Paul and Bunnell test for heterophile antibodies, also the technic for the quantitative determination of plasma proteins, proteins in cerebrospinal fluid and other body fluids, and the forensic

applications of blood grouping. Among the major additions from the original investigations of the author and his co-workers are new data on the normal values for plasma proteins, for the renal threshold, for the erythrocyte count, hemoglobin, cell volume, color, volume and saturation indexes, total and differential leukocyte counts, sedimentation rates, reticulocyte count and sternal marrow. The improved technic for reticulocyte counting, methods for accurate prognosis from changes in neutrophil morphology and a simple clinical method for obtaining sternal marrow during life are further additions. New data on the histogenesis of the monocyte and plasma cell derived from a study of monocytic and plasma cell leukemias are also included from our work. Special attention has been given both in the text and in the Index by Diseases to the new development in the diagnosis of such conditions as hyperinsulinism, hyperparathyroidism, infectious mononucleosis, erythroleukoblastosis, teratoma testis, iron deficiency anemias, etc." (From the Author's Preface.)

DISEASES OF THE THYROID GLAND. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas. With a Chapter on Hospital Management of Goiter Patients by VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 348; 181 illustrations. Third edition, entirely rewritten. St. Louis: The C. V. Mosby Company, 1935. Price, $7.50.

IN this, as in previous editions, the author presents the results of his personal experience with thyroid disease, and his highly individual opinions (often unique) concerning its clinical and pathologic aspects. No attempt is made to reflect generally prevailing views of the subject. There is little reference to the literature and no bibliography; there is occasional evidence of careless writing. The increasing importance of the endocrine interrelationships of the thyroid is practically ignored. The classification of goiter (of which too many already exist) is vague and confusing, and many of the illustrations are of little value. The drawings illustrating surgical anatomy and technique are good. The book is not a valuable contribution to the literature of thyroid disease. E. R.

DISORDERS OF THE BLOOD. Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), D.P.H., Assistant Pathologist, the Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (NEW ZEALAND), Assistant Pathologist, The Christchurch Hospital, New Zealand; Late Postgraduate New Zealand Scholar, The Middlesex Hospital, and Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital. Pp. 543; 53 illustrations and 12 plates (8 in colors). Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $7.00.

IN few fields of clinical medicine have the accumulation of new facts and the comprehension of disease pictures increased more rapidly in recent years than in hematology. This has naturally been reflected in the number of new books that have appeared on the blood and its disorders, one of the best being this latest contribution to the subject from the Middlesex Hospital. The extensive hematologic literature of the past decade—especially in England, Germany and this country—has been thoroughly and discriminately covered, to produce a work that covers not only the outlines of normal and pathologic hemolytopoiesis but also the various disorders of

the blood, their nature, diagnoses and treatment. Especially are the more recent advances comprehensively and comprehendingly presented. On many undecided points the prevalent view is the one regularly presented, but attention is as regularly called to the minority standpoint. A convenient novelty is the insertion of Summaries at the ends of most of the chapters. A final chapter (52 pages) on technique includes determinations of blood volume, grouping, spectroscopy, bone-marrow biopsy, as well as the usual hematologic methods. E. K.

ARCHIVOS DE MEDICINA LEGAL E IDENTIFICAÇÃO. Official Publication of the Institute of Identification. Edited by LEONIDIO RIBEIRO, M.D., Director of the Institute of Identification. Vol. V, No. 11. Pp. 212; illustrated. Rio de Janeiro: Imprensa Nacional, 1935. (No price given.)

ONE of the outstanding institutions in the field of criminology from the medical standpoint is the Institute of Identification in Rio de Janeiro. Its eminence is largely due to its organizer and director, Dr. Ribeiro, who in 1933 was awarded the Lombroso Prize by the Royal Academy of Medicine in Rome. The contents of this issue of the Archives of Legal Medicine and Identification pay high tribute to the excellent investigative and educational work being carried on in the Institute. Of particular interest is Dr. Ribeiro's article on the "Ability of Leprosy to Alter the Designs of Finger Prints." R. K.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. EIGHTH SESSION. Herausgegeben von PROF. DR. EB. KOCH, Bad Nauheim. Pp. 262; 80 illustrations. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 15.

FOR this eighth annual session, held at Wiesbaden, the main topic of "Circulation and Respiration" was selected. The three chief articles are by Hess, of Zurich, on the Physiologic Interplay of Circulation and Respiration; by Wenckebach, of Vienna, on Disturbances of Respiration and Their Influence on the Circulation; and by Hochrein, of Leipzig, on the Pulmonary Circulation Under Normal and Pathologic Conditions. Other well-known authors are among the 35 contributors to the program, the last 11 items of which are on miscellaneous topics. The general level of excellence appears to be up to former standards. E. K.

FOOD AND BEVERAGE ANALYSIS. By MILTON A. BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Department of Correction Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island; Clinical Professor of Medicine and Lecturer in Therapeutics, New York Post-Graduate Medical School, Columbia University, etc. Pp. 246. Philadelphia: Lea & Febiger, 1935. Price, $3.50.

OVER 3200 analyses of nutritive values, over 400 iodin analyses, 350 analyses of vitamins and the analyses of over 500 foods for their content of various minerals make this little volume the outstanding publication in its field. Noteworthy is the inclusion of numerous analyses of canned and packaged, *i. e.*, commercial foods, thereby greatly enhancing the practical value of the information. The data are conveniently presented in tables, with alphabetical listing of foods and with not only the percentage compo-

sition of the nutritive elements but also the number of grams of each element in a specific portion (based on household measure) of the food. The book will prove valuable to everyone who deals with any phase of practical dietetics. R. K.

A TEXT-BOOK OF FRACTURES AND DISLOCATIONS. Covering Their Pathology, Diagnosis and Treatment. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Clinical Surgery, Rush Medical College of the University of Chicago; Attending Surgeon, Presbyterian Hospital, etc. Pp. 1000; 1042 illustrations. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $11.00.

THIS third edition of Speed's excellent book on fractures and dislocations is welcomed by those practitioners and surgeons who treat fractures. The plan of the original edition has been preserved. Each fracture is treated as a complete unit, with a description of the anatomy, the cause and incidence of the fracture, pathology, complications, symptoms and diagnosis, and then a full discussion of the standard methods of treatment. The methods suggested are not always the most advanced, but they are those which have been tried and proved useful in an extensive fracture experience. At the end of each section there has been appended in this edition a list of references for the use of students and surgeons who wish to investigate the literature further. The illustrations are in many cases excellent actual photographs or tracings from roentgenographs. The work will be found to be an indispensable standard reference for surgeons and students.

L. F.

PRECIS DE PATHOLOGIE EXTERNE. In 2 volumes. By PROFESSOR E. FERGUE. 9th edition. Pp. 2370; 1164 illustrations and 4 plates. Paris: Gaston Doin & Cie. Price, paper, 180 francs.

THIS precis, awarded the Godard prize by the Academie de Médecine in 1903, now appears in its ninth edition. The author has brought together material seldom if ever presented in an American or English text of comparable length. Though a counterpart of our textbooks of surgery, it presents pathologic processes, particularly the common surgical conditions, from the viewpoint of the preclinical sciences. To this is added an excellent presentation of symptomatology and diagnosis. Treatment is outlined briefly, though the paragraphs devoted to it are more suitable as references than as descriptions. The emphasis is distinctly French and in many instances is quite different from that of English and American authors.

J. R.

VIER VORLESUNGEN ÜBER KREISLAUFFRAGEN. Gehalten an der Spanischen Universidad International de Verano en Santander. By DR. BRUNO KISCH, ordentlicher Professor der Physiologie an der Universität Köln. Pp. 64; 6 illustrations. Köln: Paul Kuschbert, 1934. Price, Rm. 3.60.

THESE lectures given in the Casa de Salud at Santander deal with rather specialized recent fields of cardiac functional pathology, chiefly with the humoral changes in the blood in heart disease. In the first, on "Circulation and Metabolism," the lecturer considers how the circulation and the blood content change in various normal conditions and in heart disease and how this in turn affects the heart and the other viscera. In the second lecture on "Humoral Blood Changes in Circulatory Insufficiency," the importance of the circulation in regulating bodily activity is stressed. "The Circulation and the Autonomic Nervous System" (third lecture)

offers numerous examples of the importance in the economy of the organism of the "life nerves," which in vital organs are always beyond voluntary control. In the last lecture, on "The Irradiation of Autonomic Reflexes," is expounded the author's law: "In the domain of the automonic nervous system . . . reflexes (exclusive of axone reflexes) are never limited to a single reflex zone." These lectures should be of interest and value especially to those concerned with the special field that they cover. E. K.

ARTHRITIS AND RHEUMATOID CONDITIONS. Their Nature and Treatment. By RALPH PEMBERTON, M.S., M.D., F.A.C.P., Professor of Medicine in the Graduate School of Medicine, University of Pennsylvania; Physician to the Abington Memorial and Bryn Mawr Hospitals, etc. Pp. 455; 69 illustrations, 60 tables and a colored plate. Second edition, thoroughly revised. French translation of first edition, 1933. Philadelphia: Lea & Febiger, 1935. Price, $5.50.

THE reader will find here an authoritative and complete statement of our present knowledge on the subject, a knowledge to which the author, in upwards of 20 years of study of this disease, has made valuable contributions. The appearance of this second edition, as well as a translation of the first into French, bear witness to the deserved popularity of the work. R. K.

A MARRIAGE MANUAL. A Practical Guide-Book to Sex and Marriage. By HANNAH M. STONE, M.D., Medical Director of the Birth Control Clinical Research Bureau and of the Marriage Consultation Centers at the Community Church and Labor Temple, New York, and ABRAHAM STONE, M.D., Adjunct Urologist at the Sydenham Hospital; Co-Director of the Marriage Consultation Centers at the Community Church and Labor Temple, New York. Pp. 334; 8 illustrations. New York: Simon and Schuster, 1935. Price, $2.50.

THE book fully lives up to its subtitle: it is practical, accurate and instructive. Emphasis and clarity have been heightened by the form of presentation: questions and answers between a young couple and the physician. Doctors will find this an excellent book to recommend to their patients. R. K.

THE DISEASES OF THE ENDOCRINE GLANDS. By HERMANN ZONDEK, M.D. (BERLIN), Director of the Medical Division, Bikur Cholim Hospital, Jerusalem, etc. Pp. 492; 168 illustrations. Third edition, revised and enlarged. Translated by CARL PRAUSNITZ, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Honorary Research Fellow, Victoria University of Manchester, etc. Baltimore: William Wood & Co., 1935. Price, $11.00.

THIS book cannot be recommended as it is full of speculative and unsound conceptions and unwise therapeutic recommendations.

A few examples speak for themselves: Osteomalacia, instead of being accepted as essentially due to deficiency in vitamin D, is regarded by the author as an endocrine disorder. He believes that excessive parathyroid function can produce osteomalacia "either directly or indirectly through the medium of the ovaries" (p. 357), and that severe cases of osteomalacia require surgical removal of the ovaries. Fortunately, however, he advises vitamin D administration, but explains that "the action of vitamin D is known to resemble that of parathormone in many respects,

especially as regards calcium metabolism" (p. 360). Although there is good evidence that generalized osteitis fibrosa is due to excess parathyroid function, the author advises treating this condition with parathormone "in order to stimulate production of osteoblasts and formation of new tissues," and yet also advises what others advocate, removal of a parathyroid tumor if it is present.

He states: "The ultimate reason for the enhanced metabolism in Graves' disease must be referred to constitutional peculiarities of the tissues, chiefly the muscles" (p. 136). He believes in a "peripheral" origin of Graves' disease due to disturbances in "ionic balance in and around cells" of muscles and other tissues which are "constitutionally supersensitive to thyroid hormone." For Graves' disease, he has found beneficial in some cases pituitrin, insulin, liver extract, vitamin A to restore the disordered liver function, and calcium, in addition to the more conventional treatment.

"Occasionally it is necessary to attune the tissues to the hormone by altering their physicochemical conditions. This may be done, *inter alia*, by spa treatment (*e. g.*, Karlsbad, Marienbad, Vichy), by diet, and protein therapy" (p. 106).

He recommends administering tuberculin in Addison's disease due to tuberculosis. He has used insulin in Simmonds' disease, although we know that such patients are likely to have spontaneous hypoglycemia. He believes he is giving anterior pituitary hormones when he is giving prolan.

"Hæmatopoiesis and the distribution of the blood within the body are regulated essentially by the thyroid hormone. . . . . The hormone evidently influences the complex system regulating the composition of the blood, *viz.* bone marrow, spleen, liver, etc." (p. 39). I. Z.

SYPHILIS, IHR BIOLOGISCHER URSPRUNG UND DER WEG ZU IHRER AUSROTTUNG. By DR. MED. FERDINAND THUGUT. Pp. 109. Stuttgart: FERDINAND ENKE, 1931. Price, Rm. 4.00.

THE brochure, "Die Weltgeissel Syphilis," which appeared in 1926, proposed an ingenious theory of the origin of syphilis on the basis of recent studies on the mutability and changing virulence of the Spirochæta pallida. The author accepts the scarcely tenable view that syphilis, as we know it now, did not exist either in Europe or America before Columbus' time. It is possible, according to him, that the ancestor of the Spirochæta pallida, a harmless organism, was rendered highly pathogenic as a result of passage through new hosts. The eradication of syphilis according to the author depends on early diagnosis and treatment as well as individual prophylaxis. Written in a rather literary style this work makes interesting if difficult reading. J. S.

THE THEORY AND PRACTICE OF ANAESTHESIA. By M. D. NOSWORTHY, M.A., M.D., B.CH. (CANTAB.), Anesthetist to Westminister Hospital and Grosvenor Hospital for Women, etc. With a Foreword by I. W. MAGILL, M.B., B.CH. (BELFAST), Senior Anesthetist to Westminister Hospital, etc. Pp. 223; 35 illustrations. London: Hutchinson & Co., Ltd., 1935. Price, 12/6.

THIS small book gives the anesthesia essentials which the author has found valuable in teaching. Short chapters on the physiology of anesthesia precede chapters on anesthesia proper. Ether, chloroform, ethyl chlorid and nitrous oxid are discussed separately. The difficulties and dangers of anesthetic administration are pointed out and the author describes his methods for avoiding them. Short reference is made to the newer general

anesthetics: ethylene, cyclopropane and vinethene. Endotracheal anesthesia is described in detail. The discussion of spinal anesthesia (percain and stovain) is interesting to American surgeons. A chapter on the choice of anesthetic agents deals largely with the choice of the anesthetic in relation to the operation, rather than the choice in relation to the patient.

The book is too small to be considered anything more than a handbook for use in teaching anesthesia to beginners. The ideas expressed are largely those of the English viewpoint, which differ in many particulars from those in common usage in America. L. F.

ANEMIAS Y ALIMENTACIÓN. The Anti-anemic Principle of Liver and the Qualitative Factors of Foods (Vitamins, Ammo Acids, Iron and Copper). By JOSÉ SANCHEZ RODRIGUEZ, M.D. With a Foreword by PROF. GREGORIO MARANÓN. (Doctorate thesis, awarded the prize by the National Academy of Medicine, Spain, in 1935.) Pp. 165; 22 illustrations. Madrid: Ediciones del Arbol, 1935. Price, 12 pesetas.

THE author first reviews the development of our knowledge of the nature and causation of the anemias. He emphasizes that a proper conception of the subject must be based on an understanding of the biochemistry of erythropoiesis, and offers a physiopathologic classification of the anemias. Turning then to a consideration of pernicious anemia, he takes up as his major problem an investigation of the nature of the antianemic factor of a concentrated and purified liver extract for parenteral administration. He concludes that his extract does not contain iron, copper, the hematopoietic amino acids, the fat-soluble vitamins A, D and E, the water-soluble vitamins B_2 and C (thus differing with Castle and others who sought to identify the antianemic factor with B_2). It does contain the antineuritic vitamin B_1 in large amounts, but the failure of B_1 to cure pernicious anemia precludes it from being the antianemic factor. The author, therefore, concludes that one has to do with a new "antianemic vitamin," derivable probably from various sources and stored in the liver. The work should be of great interest to hematologists.

R. K.

METHODS AND MATERIALS OF HEALTH EDUCATION. By JESSE FEIRING WILLIAMS, M.D., Teachers' College, Columbia University, and FANNIE B. SHAW, M.A., University of Florida. Pp. 331; illustrated. New York: Thomas Nelson & Sons, 1935. Price, $1.65.

IN addition to the methods and materials of health education, the authors also discuss the philosophy of education in the light of the newer concepts of the child. Considerable space is devoted to the definition of terms in order to dispel the confusion wrought in the past by ambiguous or loose terminology in this field. Many of the older criteria of health, such as the height-weight standards, are dismissed and more adequate tests suggested. Many data and references are given to help the teacher to a clearer understanding of the physiologic and psychologic background of health and disease in the child. Several chapters on the problems of health in the school give an outline of the measures required for healthful school living. The final chapter is devoted to the health of the teacher. While some important subjects are dismissed with mere mention, the authors usually refer to publications where further details can be found. The problems of sex in relation to health education are not mentioned, and mental hygiene is discussed in one paragraph. However, the book should be of value to those interested in the education of youth. S. H.

DISEASES OF THE SKIN. By FRANK CROZER KNOWLES, M.D., Professor of Dermatology, Jefferson Medical College; Dermatologist to the Jefferson, the Pennsylvania, the Presbyterian and the Babies' Hospitals, etc. Pp. 640; 240 illustrations and 11 plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $6.50.

THERE are several highly original features about this third edition which give it distinction among most American texts on dermatology. First, the large section devoted to general dermatology, of which 35 pages are devoted to treatment. This section also includes such newer subjects in pathology as blood grouping, the endocrines, red cell sedimentation tests and clinical spectroscopy. Another distinctive feature is the freshness of the subject matter throughout the book, including such new and well-established entities as erythroplasis, tularemia, Habermann's syndrome, carotinoid pigmentation, necrobiosis lipoidica diabeticorum, ninth day erythema and the Senear-Usher syndrome. Corollary to this is the freshness of the references to the literature in which those dated 1935 are conspicuous. Illustrations are abundant and uniformly good. It is an ideal text for the medical student and the busy practitioner of general medicine.

F. W.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. A Working Manual of Clinical Pathology. By JAMES CAMPBELL TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Section on Clinical Laboratories, Mayo Clinic. Pp. 792; 370 illustrations, 29 in colors. Eighth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

THE 8 editions that this book has achieved in 27 years are adequate evidence for the leading position that it has assumed in the field of clinical diagnosis. One of the most active specialties in medicine, it is constantly producing new methods and utilizing advances in borderline subjects, and has even reached the position where its best practitioners must frequently urge caution in attaching too much importance to laboratory methods. It is no small praise to say that this edition has successfully kept abreast with these advances.

E. K.

DIE WERKE DES HIPPOKRATES. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würburg. Book 11 (price, Rm. 8; pp. 103): Die Epidemischen Krankheiten (Die Volkskrankheiten) (The Epidemic Diseases (Diseases of the People)), 1.–3. Book. Book 12 (price, Rm. 9.50; pp. 135): Die Epidemischen Krankheiten (Die Volkskrankheiten) (The Epidemic Diseases (Diseases of the People)), 4.–7. Book. Stuttgart: Hippokrates Verlag G.M.B.H., 1934. (To be published in 25 parts, costing *ca.* Rm. 100, card binding.)

THESE two sections include in 7 books the notes on epidemic diseases which Hippocrates prepared toward a treatise on epidemiology. They may be regarded as successors to his work on public hygiene, "Air, Waters and Places" (Part 6 of this collection). It seems that in long visits to various islands and coastal towns of the Ægean Sea where he was favorably received, Hippocrates and his retinue of students made copious notes on "wax tablets and leather sheets." These about 323 B.C. reached the library at Alexandria from which copies soon penetrated throughout the civilized world. As examples of the contents, in the first book the "constitutions" and diseases of the town of Thasos are described in successive years, with

a section on 16 clinical histories; in the second, the diseases of Kranon and Perinthos are considered from both the individual and epidemiologic standpoint, while the third is a collection of 12 case histories, and so on through four more books. In spite of the unedited, rough character of the notes (especially in the fifth and seventh book)—sometimes even composed of ungrammatical sentences, as the translator and annotator, Stricker, points out—the disease pictures stand out so sharply that they can almost without exception be identified today. Littré's text has been followed in the translation, with modifications as suggested by the studies of Ilberg and Kuhlewein, Wenkebach, and Rudolf Herzog. E. K.

NEW BOOKS.

The Cerebrospinal Fluid and Its Relation to the Blood. A Physiological and Clinical Study. By SOLOMON KATZENELBOGEN, M.D., Associate in Psychiatry, in charge of The Laboratory of Internal Medicine, The Henry Phipps Psychiatric Clinic, The Johns Hopkins Medical School, etc. Pp. 468; 48 tables and 20 charts. Baltimore: The Johns Hopkins Press, 1935. Price, $5.00.

The Parathyroids in Health and in Disease. By DAVID H. SHELLING, B.Sc., M.D., The Johns Hopkins University and Hospital, Baltimore. Pp. 335; 26 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $5.00.

New Pathways for Children with Cerebral Palsy. By GLADYS GAGE ROGERS, Director of Robin Hood's Barn, A Camp School for Children with Cerebral Palsy, and LEAH C. THOMAS, Director of Therapeutics at Robin Hood's Barn, etc. With Photographs by NEWELL GREEN. Pp. 167; 12 illustrations. New York: The Macmillan Company, 1935. Price, $2.50.

Modern Office and General Practice. A Handbook of Practical Medicine. By DEANE R. BRENGLE, M.D. Pp. 320; illustrated. Kingsport, Tenn.: Southern Publishers, Inc., 1935. Price, $3.25.

Immunology. By NOBLE PIERCE SHERWOOD, PH.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kans. Pp. 608; 27 illustrations, 8 colored plates, and many tables. St. Louis: The C. V. Mosby Company, 1935. Price, $6.00.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Eighth Session. Herausgegeben von PROF. DR. EB. KOCH, Bad Nauheim. Pp. 262; 80 illustrations. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 15. (Review p. 280.)

International Clinics. Vol. IV, Forty-fifth Series, December, 1935. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 331; illustrated; 2 colored plates. Philadelphia: J. B. Lippincott Company, 1935.

The Patient and the Weather. Vol. 1, Part 1, The Footprint of Asclepius. By WILLIAM F. PETERSEN, M.D. Pp. 127, lithographed; 94 illustrations. Ann Arbor: Edwards Brothers, Inc., 1935. Price, $3.75.

Klinik und Therapie der allergischen Krankheiten. By DR. ERICH URBACH, Privatdozent für Dermatologie an der Universität Wien; I. Assistant der Universitätsklinik für Geschlechts- und Hautkrankheiten in Wien (Vorstand PROF. DR. W. KERL). Pp. 781; 302 illustrations (26 in colors) and 24 tables. Wien: Wilhelm Maudrich, 1935. Price, Rm. 30.

Pollen Grains. Their Structure, Identification and Significance in Science and Medicine. By R. P. WODEHOUSE, PH.D., Scientific Director of the Hayfever Laboratory, The Arlington Chemical Company, Yonkers, N. Y. Pp. 574; 123 illustrations, 14 plates. New York: McGraw-Hill Book Company, Inc., 1935. Price, $6.00.

Données anatomiques en vue de la chirurgie réparatrice mammaire. By DR. CLAOUÉ et I. BERNARD. Pp. 58; 36 illustrations. Paris: Librairie Maloine, 1935. (No price given.)

Der Geburtstod (Mutter und Kind). By DR. SIGISMUND PELLER. Pp. 110; 56 tables. Wien: Franz Deuticke, 1936. Price, M. 5.

Royal Treatment in Cardiovascular Disease. By PIERRE NOËL DESCHAMPS, M.D. (Paris), Assistant Physician in Charge of the Cardiological Department, Lariboisière Hospital, Paris. Pp. 108. Baltimore: William Wood & Co., 1935. Price, $2.00.

The object of this book "is to make known to the English-speaking medical public the benefits to be derived from thermal carbon dioxide treatment," which seem to the author to be fundamental in the treatment of disturbances of the heart and vessels.

Hugh Owen Thomas. His Principles and Practice. By D. MCCRAE AITKEN, M.A., M.B., CH.B. (ED.), F.R.C.S. (ED. and ENG.), Director of Surgery, Robert Jones and Agnes Hunt Orthopædic Hospital; Senior Surgeon, St. Vincent's Orthopædic Hospital, etc. Pp. 96; 1 illustration and 8 plates. New York: Oxford University Press, 1935. Price, $4.25.

Autobiography Sigmund Freud. Translated by JAMES STRACHEY. Pp. 153; 1 illustration. New York: W. W. Norton & Co., Inc., 1935. Price, $2.00.

A Doctor's Odyssey. A Sentimental Record of LeRoy Crummer: Physician, Author, Bibliophile, Artist in Living, 1872–1934. By A. GAYLORD BEAMAN. With a word in Memory by A. EDWARD NEWTON and numerous memoirs and appreciations. Pp. 340; 21 illustrations. Baltimore: The Johns Hopkins Press, 1935. Price, $2.50.

NEW EDITIONS.

Principles of Bacteriology. By ARTHUR A. EISENBERG, A.B., M.D., Director of Laboratories, Sydenham Hospital, New York, and MABEL F. HUNTLY, R.N., M.A., Director of Nursing, Wesson Memorial Hospital, Springfield, Mass. With annotations and a section on Microbic Variations by F. E. COLLEN, M.S., PH.D., Professor of Bacteriology, Vocational School, Milwaukee. Pp. 378; 90 illustrations, and 8 colored plates. Sixth Edition. St. Louis: The C. V. Mosby Company, 1935. Price, $2.75.

Infant Nutrition. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAMS MCKIM MARRIOTT, B.S., M.D., Professor of Pediatrics, Washington University School of Medicine; Physician in Chief, St. Louis Children's Hospital. Pp. 431; 27 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $4.50.

Diseases of Women. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine; Gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, and St. Luke's Hospital, etc., and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Pp. 999; 1058 illustrations, including 1 colored plate. Eighth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
I. S. RAVDIN, B.S., M.D.,
J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,
AND
C. G. JOHNSTON, M.S., M.D.,
INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

SURGICAL DISEASES OF THE PANCREAS.

Not so many years ago the pancreas was thought to be practically unapproachable. Even as late as 1932, Heyn,[1] speaking of the treatment of hyperinsulinism, stated that the treatment was medical unless "increasing amounts of carbohydrate became necessary; then surgery, even if unsuccessful, must be tried" and that for the present "surgery appears not to be good enough." This attitude was not universal as evidenced by the striking results which we shall mention later, but there is rather generally still some apprehension regarding operative interference in diseases of the pancreas.

During the past decade there has been a renewed interest in the surgical approach to diseases of the pancreas. This has been chiefly concerned with the treatment of hyperinsulinism. The strikingly good results in the condition of patients from whom adenomata of the pancreas have been removed indicate the importance of this form of therapy. Whipple and Frantz[2] report 19 cases operated on by 10 different surgeons with no deaths, an indication that the mortality following this type of surgery need not be high.

One reason for the caution in attempting surgical treatment of pancreatic lesions lies in the anatomy and structure of this gland. Lying in the posterior portion of the abdomen in a retroperitoneal position, the pancreas is shielded from approach posteriorly by the great muscles of the back, the spine, the portal vein, the aorta, the left kidney and its vessels, and the pillars of the diaphragm. Thus it is seen that though the posterior surface of the pancreas is extraperitoneal it is inaccessible from the posterior approach because of these important structures. The anterior approach is complicated by

the depth of the organ, its position behind the stomach, and its close association with the duodenum and spleen.

The bloodvessels of the pancreas form a broad anastomosis, the branches of the celiac axis providing the major portion of the blood supply, the superior mesenteric supply the inferior pancreaticoduodenal and inferior pancreatic arteries. The gastroduodenal artery gives rise to the superior duodenal, the splenic artery to the superior pancreatic artery. The vessels form a circle about the pancreas. The blood supply of the pancreas is intimately associated with that of the duodenum, the stomach and the spleen. The veins of the pancreas empty into the portal, superior mesenteric and splenic veins, the drainage being finally into the liver through the portal vein. The distribution of the vessels of the pancreas has been studied recently by Wharton.[3]

In addition to studying the gross distribution of the vessels, Wharton studied the finer branches and anastomoses within the pancreatic tissue. The arterial plexus is formed from the circle of vessels supplying the gland, a single artery entering a lobule and dividing to form a glomerular-like structure of a sinusoidal nature among the cells of the islands of Langerhans. From these sinusoids small vessels pass into the interacinar capillary network. It can be seen from Wharton's[3] description that the blood stream widens markedly, so that the islands of Langerhans are bathed in a slow stream of blood. In addition to the clear description of his own studies, Wharton reviews and discusses the work of earlier investigators on the blood supply of the pancreas.

Besides the rich blood supply, another factor which commands gentleness of manipulation of the pancreas is its friable lobular structure. When torn across, the pancreas presents potentialities of drainage of material with a high enzymatic content which can cause liquefaction and fat necrosis of the surrounding tissues.

The external secretion of the pancreas, which is rich in digestive ferments, reaches the duodenum through the main duct, the duct of Wirsung, which traverses the entire length of the gland to join, as a rule, the common bile duct just proximal to the ampulla of Vater. Usually an accessory duct, the duct of Santorini, communicates with the main duct within the pancreas and empties into the duodenum at a point above the entrance of the main duct. There have been many variations noted in the ductal system of the pancreas. At times the accessory duct has no connection with the duodenum. When there is an obstruction at the ampulla of Vater the accessory duct may be the only functioning outlet and it is possible for all the external secretion to pass through it.

The lymphatic drainage of the pancreas, according to Bartels,[4] is into four groups of lymph nodes: 1, at the hilus of the spleen; 2, on the superior portion of the pancreas; 3, on the inferior surface of the pancreas; and 4, at the head of the pancreas. It is concerning this last group of nodes that much controversy has arisen with regard to the etiology of acute pancreatitis. It must be kept in mind that into these lymph nodes drain not only the pancreas but also the spleen, stomach, duodenum and hepatic structures.

The two surgical diseases of the pancreas most commonly met with

are carcinoma, usually situated at the head, and pancreatitis. About the etiology of acute pancreatitis much has been written. The occurrence of acute pancreatitis in association with gall bladder disease for many years suggested that possibly acute pancreatitis was the result of infection which had spread from the gall bladder to the pancreas through lymphatic channels. Deaver and Pfeiffer,[5] Sweet,[6] and Graham and Peterman[7] have presented evidence in its favor. Graham and Peterman injected bacteria into the portal vein and traced the infection from the liver to the gall bladder and thence by lymphatic extension to the nodes lying at the head of the pancreas. Inflammatory changes were also found in the pancreas. Kauffman[8] repeated some of the experiments of Graham and Peterman and confirmed the findings of lymphadenopathy in the nodes at the head of the pancreas but, except in cases where a blood stream infection or contact inflammation was present, found no evidence of pancreatitis. Kauffman argues that the lymphatic drainage is away from the area and the valves in the lymphatic channels would prevent backflow. His results would tend to deny the possibility of extension of infection in the gall bladder to the pancreas by lymphatic channels, a concept which has for many years been quite generally accepted. It is only the occasional case in which pancreatitis is found not associated with signs of inflammatory process in the gall bladder. Whether or not the extension of inflammation from the gall bladder to the pancreas by the lymphatics is the explanation of the etiology of acute pancreatitis, the association of inflammation in these two organs is too common to pass by without further proof that this theory is not tenable in some cases at least.

The close association of the common bile duct and duct of Wirsung suggests the possibility of the passage of bile into the pancreas when the ampulla of Vater is obstructed. Many attempts have been made to produce acute pancreatitis experimentally by injecting bile into the ducts. Opie[9] produced pancreatitis by the injection of bile into the pancreatic ducts, but it was necessary to inject as high as 5 cc., which is enough to cause distention of the ducts and so introduce an added factor of trauma. Pancreatitis has been produced by the injection of bile salts into the pancreatic duct but this is not wholly physiologic. Archibald[10] believes that it is the entrance of altered bile into the pancreatic ducts which produces the damage, normal bile causing but a transient edema. Other causes are advanced to explain inflammatory changes in the pancreas, notably trauma, action of digestive ferments in the pancreas and toxic changes following systemic disease.

If the causes of acute pancreatitis are difficult to ascertain, the diagnostic criteria are even more difficult to determine. A careful perusal of the literature will emphasize that the diagnosis of an inflammatory lesion of the pancreas is made more often at operation or necropsy than pre-operative. De Takats and MacKenzie[11] report 6 cases of acute pancreatitis, none of which was diagnosed prior to operation. In McWhorter's[12] series the diagnostic accuracy was 12%. Most commonly the diagnosis of perforated peptic ulcer or acute cholecystitis is made. Most of the patients found to have acute pancreatitis have had previous histories of abdominal pain and attacks described under the general term of indigestion, which may be interpreted as mild

attacks of pancreatitis or as evidence of conditions so frequently associated with acute pancreatic lesions. The pain associated with acute pancreatitis is, as a rule, severe enough to be prostrating, sudden in onset and, as a rule, persistent despite the administration of morphin. The most common position of the pain is in the epigastrium, though it has been reported as localized in every portion of the abdomen and at times widespread. Pain in the back likewise has been reported, as well as in either shoulder blade. Generalized rigidity is common but, as a rule, it is not the boardlike rigidity of a perforated ulcer. Tenderness, like the pain and rigidity, varies as to intensity and position. Vomiting is practically always present and is difficult to control. Early in the attack the temperature may be normal or subnormal, but it usually rises later. The white blood count is increased from 15,000 to 30,000. The blood sugar may be elevated and sugar may appear in the urine, but this is not common. The determination of amylase in the urine[13] and in the serum[14] is said to be diagnostic. These tests are seldom carried out and, due to difficulties of standardization, have not become popular. There appears to be a sound basis for the application of these tests in suspected cases since damage to the pancreas has been shown to cause a marked rise in serum and urinary diastase (personal observations). If the amylase determinations are to be worth much they must be carried out early in the course of the disease as after a rather short period, 1 to 3 days, normal values will be found. The Cammidge and Loewi tests, described as diagnostic tests for pancreatitis, are more difficult to explain on a rational basis.

Aspiration of the abdominal cavity has been suggested as a diagnostic measure, the finding of "beef broth" fluid being stated by Forbes[15] to be diagnostic. This procedure is not without hazard and the abdominal fluids found at operation have not been uniform in consistency or color.

The cause for the small number of cases diagnosed correctly before operation is not far to seek when one considers the variations in the clinical picture. The symptoms are likely to lead to a diagnosis of one of many acute abdominal inflammatory processes and the diagnosis is more likely to be made if the signs and symptoms of the condition most suspected are not clearcut.

In regard to treatment, most surgeons operate and drain the pancreas as early as possible. This feeling is not held universally, since Eliason and North[16] and Mikkelson[13] advise palliation. The mortality of the cases operated on is quite high—approximately 60%. Mikkelson reports a mortality of 7.5% in a series of 39 cases. It is difficult to determine the mortality of cases not operated on due to the difficulties of diagnosis, so that many may be diagnosed acute pancreatitis which are not definitely proven. The major difficulty in conservative treatment lies in the exclusion of perforation of a hollow viscus, since it might prove fatal to delay operation in these cases. The operation, as a rule, consists of drainage of the pancreas or an abscess if present. Drainage of the gall bladder or common duct is also advocated.

Acute pancreatic inflammatory lesions, whether they be of infectious nature or due to vascular changes in the pancreas, present symptoms of a severe nature which direct immediate attention to them and sug-

gest the serious nature of the illness. That the pancreas may undergo mild inflammatory changes with repeated recurrences is a possibility that has long been evident in medical and surgical thought. Many of the cases of so-called chronic pancreatitis have never been proven to have true inflammatory lesions of the pancreas. It is rather hard to determine the type of chronic inflammatory lesion which could cause the smoldering type of symptoms associated with this entity. Let it be said at the outset that those who speak of chronic pancreatitis do not have in mind any of the chronic granulomatous lesions, but think generally in terms similar to those associated with chronic appendicitis, a condition which many feel does not exist. The presence of fibrosis alone cannot be taken as evidence of chronic inflammation, but rather evidence of a previous acute inflammation or of vascular changes. The diagnosis of chronic pancreatitis is usually made at operation by feeling the head of the pancreas. If it feels larger and firmer than is usually considered "normal," in the presence or absence of gall bladder disease or a dilated common duct, this diagnosis is apt to be made. This basis of diagnosis is generally considered as the most convincing but the diagnosis depends on the experience of the surgeon and his ability to ascertain by the sense of touch actual changes in the head of the pancreas.

Gruber,[17] in a discussion of chronic pancreatitis, (Henke and Lubarsch[18]), states that the entire pancreas may be as hard as cartilage and yet show no evidence of acute or chronic inflammation. He quotes Heiburg as stating that it is impossible to determine the presence of chronic inflammation in the pancreas without examination microscopically. He further states that in reply to a questionnaire directed to surgeons by Guleke, it was found that some surgeons had seen but 10 to 20 cases in a 14-year period, one reported as many as 400 cases, and yet another stated that he had observed "numberless" cases.

De Tarnowsky and Sarma[19] state that the symptoms are in general those of biliary tract stasis. It is evident that the enlargement of the head of the pancreas may be considered as an associated phenomenon with lesions in contiguous or nearby structures. This viewpoint does not exclude the occurrence of a similar train of symptoms resulting from partial obstruction to the outflow of pancreatic juice or changes brought about in the parenchyma of the gland due to arteriosclerotic changes or prolonged general diseases. The question of so-called chronic pancreatitis is one which requires critical work and thought to determine the anatomic and physiologic basis for such an entity. The term pancreatitis refers to a pathologic process, the adjective "chronic" refers to the nature of the clinic course. It is necessary in order to clarify our thoughts on this subject to separate the connotations of this term and to separate as nearly as possible those cases which are primarily pancreatic in origin from those in which the pancreas is either secondarily involved or actually not involved at all.

Pancreatic lithiasis, cysts and traumatic rupture of the pancreas are fortunately uncommon. The diagnosis of pancreatic duct stone is, as a rule, made from Roentgen findings. The stones having a definite calcium content are radiopaque but may be wrongly interpreted as

calcified lymph glands. Ackman and Ross[20] review 54 cases and stress the varied symptomatology associated with pancreatic lithiasis.

With regard to rupture of the pancreas, Venable[21] reports 4 cases and presents observations gleaned from his own experience and a review of the literature. In general the problem is similar to that of rupture of other intraäbdominal solid viscera and early surgical intervention is required. The early symptoms are likely to be more severe than is the case with rupture of other intraäbdominal viscera.

The clinical features of inflammation of the pancreas offer many difficulties. The signs and symptoms, and even the classification of the pathologic processes, afford difficulties which defy any clearcut description. The symptoms which are associated with tumors of the islet tissue, however, are more readily understood and lend themselves more clearly to definition. These are in the main similar to those symptoms so commonly known by all who have had experience with insulin therapy. The conditions resulting from insulin overdosage have been common knowledge since the discovery of insulin by Banting and Best[22] in 1922, and the description of Banting and his associates[23] of the symptoms of "insulin shock." The concept that if the islands of Langerhans might be deficient in the production of insulin, so also an excess of this material might be elaborated by them, was presented by Seale Harris[24] a little over a year after the discovery of the active principle of the islands of Langerhans in a paper entitled "Hyperinsulinism and Disinsulinism."

Since Harris' paper numerous reports have appeared dealing with this subject. In recent months a most thorough review of the surgical aspects of hypersecretion has been presented by Whipple and Frantz.[2] Not only do these authors review the literature in a thorough and interesting manner, but also present a series of 6 cases with excellent results from operative intervention.

It is interesting that all of the patients reported by Whipple and Frantz were seen in the Neurological Institute where they were sent because of nervous disturbances. These consisted of spells of unconsciousness, somnolence, mental confusion, sweating, dizziness, giddiness, disorientation, diplopia and amnesia. Personality changes occurred in several. In all, there were found low blood sugar values even as low as 25 mg. per 100 cc. The symptoms were relieved after the administration of glucose, with the resultant increase in blood sugar. In all the cases a pre-operative diagnosis of islet cell tumor was made, and at operation one or more of these tumors were found. In one case after the removal of one tumor the patient's blood sugar remained low and it was necessary to reoperate and remove another tumor which had been overlooked at the first operation. The authors call attention to the fact that it is necessary to examine the pancreas carefully for other nodules, even though one is found. All these patients were relieved of their symptoms and their blood sugar values returned to and remained at normal levels.

It must be pointed out that the finding of a low blood sugar in association with neurologic symptoms or mental aberrations is not sufficient for the diagnosis of hyperinsulinism resulting from islet cell tumor. Wauchope[25] classifies the conditions which produce hypoglycemia, in addition to excess of insulin as follows: 1, lack of opposing secretions

due to disease of the adrenals, pituitary, or thyroid gland; 2, lack of glycogen due to destruction of reservoirs, as in disease of the liver, wasting of muscles; abnormal excretion of sugar, as in renal diabetes or lactation; active depletion of stores, as in muscular exercise, and failure to replenish stores, as in starvation; 3, interference with the regulating center, as in disease affecting the pons or overaction of the vagus. It is, therefore, necessary to rule out causes other than excess of insulin before an operation for the removal of an adenoma of the pancreas is considered. Common conditions suspected in the cases of adenomata of the pancreas reported in the literature are epilepsy, drunkenness, brain tumors and encephalitis. One of the patients reported from the Barnes Hospital, where the experience with hyperinsulinism has been quite extensive, was thought to have epilepsy,[26] another was thought to have a brain tumor.[27] One patient, operated on in our clinic and in whom adenoma was found, was sent to the neurosurgical service with the suggested diagnosis of a brain tumor (to be reported by Ravdin and Lukens). One of Whipple's patients, as well as one reported by McClenahan and Norris,[28] was thought to have had encephalitis.

Seale Harris[29] points out that the incidence of hyperinsulinism is greater than it is ordinarily thought to be. The severe cases presenting striking pictures and relieved by surgery certainly do not constitute the entire number of cases. Harris believes hypoinsulinism to be almost as common as diabetes. Of 3000 cases, he reports 500 cases of diabetes and 250 of hypoglycemia. Many patients have only mild symptoms and can be controlled entirely by diet. In a later paper Harris[30] points out that often the symptoms simulate various forms of gastro-intestinal disease.

The best results following surgical removal have been obtained in those patients in which adenomata have been found. Cases in which carcinomata have been found[31, 32] and in which metastases also were found were not helped by operation. The exact nature of the tumors removed from the pancreas, in the cases which obtained relief from their symptoms, is in most instances difficult to determine. Some tumors were well encapsulated but many were not. The structure of the masses removed from the 5 cases studied at Barnes Hospital has been reported by O'Leary and Womack.[33] But one of these tumors had malignant characteristics.

Following the removal of a tumor from the pancreas of a case to be reported by Ravdin and Lukens, an attempt was made to transplant some of the tissue into a diabetic with the hope that the cells would proliferate and reduce the insulin requirements of the recipient. The graft, however, was not successful. Tissue cultures were also made of the tissue in the hope that after cultivation a transplant could be effected, but these were likewise unsuccessful. A similar thought was evident in association with the cases of Whipple and Frantz,[2] as Murray and Bradley[34] reported attempts similar to ours. Direct transplantation of tissue from one patient to another has proven to be futile in the majority of instances. According to the work of Stone, Owings and Gey[35] on cultivation and transplantation of parathyroid tissue, the best chance of a successful transplant seems to lie in the transplantation of cultured tissue. Whether islet cells transplanted in this manner

will prove successful in alleviating the need for insulin therapy is problematical but it deserves further study.

Isolated tumors of islet tissue have not been found at operation in all reported cases of hyperinsulinism. Whipple and Frantz[2] emphasized the difficulties of finding adenomata, especially where the tumor lies within the substance of the pancreas. It is possible that in some instances tumors are overlooked even after a most careful search. In many of these cases a portion of the pancreas has been removed, but the results have not been gratifying. Except in a few cases the symptoms have returned following operation. Holman and Railsback[36] suggest that in order to be effective, four-fifths of the entire pancreas should be removed.

The removal of a portion of the pancreas or the excision of an adenoma is a surgical procedure of major proportions and the operation should be considered with some circumspection. The mortality following removal of adenomata of the pancreas, however, has been negligible. Whipple and Frantz[2] attribute this to the skill of the surgeons who have attempted the operation, and not to the simplicity of the operation itself. The low mortality will probably not be maintained as the popularity of the procedure increases. The importance of the experience and skill of the surgeon is emphasized by elective procedures carried out on the pancreas.

Within recent years successful attempts have been made to remove carcinoma of the ampulla of Vater by Parsons and Mullins[37] and Walters.[38] Surely this is not a procedure for the novice. Carcinoma of the ampulla of Vater produces suffering and mortality due primarily to obstruction. The growth is, as a rule, slow and metastases are late. Selected cases in the hands of a competent surgeon are offered relief from this all too common disorder by resection of the growth and contiguous structures. In the past these cases have been relieved of obstruction by cholecystogastrostomy or cholecystoduodenostomy, a purely palliative procedure. Permanent relief to patients suffering from this disturbance which heretofore has been considered hopeless seems now to be within the scope of surgical therapy if seen early.

I. S. Ravdin, M.D., and
C. G. Johnston, M.D.

REFERENCES.

1. Heyn, L. G.: J. Am. Med. Assn., **98**, 1441, 1932.
2. Whipple, A. O., and Frantz, V. K.: Ann. Surg., **101**, 1299, 1935.
3. Wharton, G. K.: Anat. Rec., **53**, 55, 1932.
4. Bartels, P.: Das Lymphgefässystem, Jena, Gustav Fischer, 1909.
5. Deaver, J. B., and Pfeiffer, D. B.: Ann. Surg., **59**, 841, 1914.
6. Sweet, J. E.: The Surgery of the Pancreas, Philadelphia, J. B. Lippincott Company, 1915.
7. Graham, E. A., and Peterman, M. G.: Arch. Surg., **4**, 23, 1922.
8. Kauffman, M.: Surg., Gynec. and Obst., **44**, 15, 1927.
9. Opie, E. L.: Johns Hopkins Hosp. Bull., **12**, 182, 1901.
10. Archibald, E.: Ann. Surg., **90**, 803, 1929.
11. De Takats, G., and MacKenzie, W. D.: Ibid., **96**, 418, 1932.
12. McWhorter, G. L.: Arch. Surg., **25**, 958, 1932.
13. Mikkelson, O.: Acta Chir. Scandin., **75**, 373, 1934.
14. Elman, E. R.: Arch. Int. Med., **48**, 828, 1931.
15. Forbes, R. D.: Western J. Surg., **40**, 425, 1932.
16. Eliason, E. L., and North, J. P.: Surg., Gynec. and Obst., **51**, 183, 1930.

17. Gruber, G. B. (quoted in Henke, F., and Lubarsch, A., Ref. 18).
18. Henke, F., and Lubarsch, A.: Handb. d. spez. path. Anat. u. Histol., Berlin, Julius Springer, **5**, Pt. 2, 396, 1929.
19. de Tarnowsky, G., and Sarma, P. J.: Ann. Surg., **191**, 1342, 1935.
20. Ackman, F. D., and Ross, A.: Surg., Gynec. and Obst., **55**, 90, 1932.
21. Venable, C. S.: Ibid., p. 652.
22. Banting, F. G., and Best, C. H.: J. Lab. and Clin. Med., **7**, 251, 1922.
23. Banting, F. G., Campbell, W. R., and Fletcher, A. A.: Brit. Med. J., **1**, 8, 1923.
24. Harris, S.: J. Am. Med. Assn., **83**, 729, 1924.
25. Wauchope, G. M.: Quart. J. Med., **2**, 117, 1933.
26. Carr, A. D., Parker, R., Grove, E., Fisher, A. O., and Larrimore, J. W.: J. Am. Med. Assn., **96**, 1363, 1931.
27. Womack, N. A., Gnagi, W. B., and Graham, E. A.: Ibid., **97**, 831, 1931.
28. McClenahan, W. U., and Norris, G. W.: Am. J. Med. Sci., **177**, 93, 1929.
29. Harris, S.: J. Am. Med. Assn., **101**, 1958, 1933.
30. Harris, S.: Am. J. Digest. Dis. and Nutrit., **2**, 557, 1935.
31. Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, H. E.: J. Am. Med. Assn., **89**, 348, 1927.
32. Judd, E. S.: Western J. Surg., **42**, 555, 1934.
33. O'Leary, J. L., and Womack, N.: Arch. Path., **17**, 291, 1934.
34. Murray, M. R., and Bradley, C. F.: Am. J. Cancer, **25**, 98, 1935.
35. Stone, H. B., Owings, J. C., and Gey, G. O.: Ann. Surg., **100**, 613, 1934.
36. Holman, E., and Railsback, O. C.: Surg., Gynec. and Obst., **56**, 591, 1933.
37. Parsons, W. B., and Mullins, C. R.: Ann. Surg., **102**, 1109, 1935.
38. Walters, W.: Surg., Gynec. and Obst., **55**, 648, 1932.

OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.,
HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,
AND
H. P. WAGENER, M.D.,
ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

OCULAR LESIONS IN DIABETES MELLITUS.

The four most commonly considered ocular complications of diabetes mellitus are: 1, transient changes in refraction; 2, cataract; 3, retinitis, and 4, toxic amblyopia. The transient changes in refraction seem to have about the same frequency under insulin as under purely dietary therapy, but are not of serious import. It seems necessary to distinguish between true diabetic cataracts and senile or presenile cataracts occurring in the diabetic. The incidence of true diabetic cataract seems to have decreased since the use of insulin. Cases of toxic amblyopia are also seen less frequently in the group of diabetics now under careful management. Lipemia retinalis is rarely seen now. However, the incidence of retinitis in diabetics has apparently increased in recent years. Even though this apparent increased incidence is attributed, as it probably should be, to the increased duration of the life of diabetics under insulin therapy, the problem of diabetic retinitis is becoming more vital to all patients with diabetes because of the serious loss of vision in many cases. The factor in the disease which is directly responsible for the retinitis has not as yet been determined. It has not been con-

clusively demonstrated that the present methods of treatment prevent the onset or control the progress of diabetic retinitis. Folk and Soskin[3] believe that proper control of the diabetes along present lines is efficacious, but Gray[5] states, on the other hand, that control of the diabetes is without effect on the retinal lesions. Because of this uncertain status of the retinal complications, several extensive studies of the eyes in diabetics have been carried out in recent years. While no definite conclusions have been reached in any of these studies, it would seem worth while to review the data obtained, particularly in the investigation carried out by Waite and Beetham.[8]

A number of different types of retinitis have been described in association with diabetes mellitus. It seems quite probable that all these types, from the central punctate retinitis of Hirschberg to the retinitis with marked disease of the veins and retinitis proliferans, represent progressive stages of the same initial lesion, complicated in some instances by changes associated with hypertension and arteriosclerosis and in the cases of hemorrhages into the vitreous and retinitis proliferans, possibly with the added factor of tuberculosis or of focal infection as pointed out by Gray. It is true, as pointed out by Folk and Soskin, that the small, punctate, deep hemorrhages in the retina and central punctate retinitis are usually associated with minimal, if any, visible changes in the retinal arterioles, and often occur in cases of diabetes without demonstrable vascular complications. Arteriolosclerosis is constantly assuming more importance in diabetes. It is probable that the occurrence of these retinal lesions is in itself evidence of vascular disease in the capillaries and probably on the venous side of the capillary loop. Also it can readily be demonstrated that other vascular complications are much more frequent in diabetic patients with retinitis than in those without retinitis. Thus, in the series reported by Wagener, Dry and Wilder,[7] the blood pressure was found to be elevated in 66% of diabetics with retinitis and in 46% of those without retinitis. A diagnosis of disease of the arteries or kidneys was made in 84% of the patients with retinitis and in 53% of those without. Diabetic neuritis, usually thought to be of vascular origin, was present in 25% of the group with retinitis, and in 8% of those without. Again, Gray found the general incidence of diabetic retinitis to be 13%, but retinitis was present in 40% of his patients with gangrene of the extremities.

Gray made a study of the intraocular arterial pressure by the dynamometer method of Baillart in 62 cases of diabetic retinitis. His findings were not uniform or conclusive. The pressure was normal in 8 cases, low in 20, and high in 34.

Waite and Beetham[8] have attempted to correlate various individual features of the retinitis with certain factors in the general disease. Thus the incidence of deep retinal hemorrhages, the feature most common to all cases of retinitis in diabetes, was found to increase definitely with increase in the age of the patients and with increase in the degree of retinal arteriosclerosis. That the occurrence of hemorrhages was not due directly to arterial hypertension was shown by the fact that considerably more than half of them occurred in patients with blood pressures within the normal and high normal range. There was no obvious causative relationship between renal disease and hemorrhages in the retina, since only 6% of the patients with hemorrhages showed blood

non-protein nitrogen values of over 44 mg. %. Yet only 18% of the patients with non-protein nitrogen values in the blood of less than 35 mg. % showed hemorrhages in the retina, while hemorrhages were present in 30% of the diabetics with non-protein nitrogen above 50 mg. %. All these facts indicate the higher incidence of hemorrhages in diabetes with complicating vascular and renal disease.

The relationship between hemorrhages in the retina and duration of the diabetes is quite definite. Thus hemorrhages were found in 6% of the cases of 1 year's duration, and in 20% of the cases of 5 to 10 years' duration, while the average age of the patients was approximately the same in each group. Hemorrhages were present in 43% of the cases of 10 to 15 years' duration and in 59% of the cases of over 15 years' duration. Thus there is a definite increase in the incidence of hemorrhages with increased duration of the diabetes disproportionate to the increased age of the patients.

That the use of insulin is apparently not a factor in causing the hemorrhages is shown by the fact that only 1.7% of the patients with hemorrhages in the retina were taking 50 units or more of insulin daily, while 4.5% of the total group of diabetics were using this amount.

No obvious relationship could be demonstrated between hemorrhages and blood calcium or blood sugar levels. Blood calcium was estimated in 9 patients with hemorrhages. It was slightly below normal in one. Only 7% of the patients with hemorrhages showed fasting blood sugars of over 300 mg. %.

Waxy exudates occurred in about 10% of the diabetics examined. Their incidence increased with the age of the patients, a sharp increase in incidence being noted in patients over 50 years of age. The exudates also increased in frequency with greater duration of the diabetes, being present in approximately 10% of the cases of 5 to 10 years' duration, in 30% of the cases of 10 to 15 years' duration, and in 40% of the cases of more than 15 years' duration. They may arise through hyalinization of deep retinal hemorrhages.

Hemorrhages in the nerve fiber layer of the retina apparently have no characteristic incidence in diabetics. They were found in 5% of the patients, and 83% of them were found in association with the characteristic deep hemorrhages. It is interesting to note that in diabetes their incidence increased with increase in the age of the patients, while, in the group of non-diabetics selected for comparison, their incidence decreased with increase in the age of the patients. Cotton-wool patches likewise showed a rising percentage by decades of life in the diabetics, and a falling percentage in the non-diabetics. They were found in 4% of the diabetics examined. Their occurrence was not related apparently to increased non-protein nitrogen in the blood. Apparently, their relationship to arterial hypertension and the relationship between retinitis and fat metabolism was not studied.

It would seem that the only definite conclusion to be drawn from these studies of Waite and Beetham is that the duration of the diabetes is more definitely a factor in the causation of retinitis than is its severity. It still seems impossible to say what feature of the diabetic disease accounts for the greater frequency of deep retinal hemorrhages in diabetics than in non-diabetics of similar age groups. Waite and Beetham think that "all evidence points to the capillaries as the source

of these hemorrhages . . . . We should seek more information about the physiology and pathology of the retinal capillaries, about their normal and abnormal hydrodynamics, about glycogen deposits which are known to affect other ocular tissues, about the normal and abnormal permeability of capillary walls, about thromboses which may form within them, and about toxins which may affect them adversely."

Waite and Beetham found in 31 of their 2002 diabetics (1.5%) preretinal hemorrhages or proliferation of vessels and connective tissue in the retina and vitreous. All of these patients were over 40 years of age, 21 of them were between 40 and 60. In 83% of this group there was marked disease of the retinal arteries and veins, which latter might be the source of the hemorrhages. The diabetes was severe in only a small percentage of the cases. The use of insulin was not connected with their development, and iodids were thought to be harmful. The prognosis is poor. Careful diabetic management does not check their progress.

The rôle of diabetes in the etiology of retrobular neuritis or toxic amblyopia is open to considerable question. Several years ago, Francis endeavored to show that ketosis was responsible. This has not been proved. The lesion may be arteriosclerotic in character. Waite and Beetham found 7 cases among their 2002 diabetics. All the patients were more than 52 years of age and showed considerable retinal arteriosclerosis. They believe, however, that the amblyopia is really due to tobacco, to which the diabetics are particularly susceptible.

The transitory changes in refraction to which the diabetic is subject at the onset of the disease and upon the initiation of treatment are of considerable interest. They are of importance, inasmuch as the occurrence of a rapid change in refraction without visible evidence of ocular disease should suggest the presence of diabetes and inasmuch as it is never wise to prescribe glasses during the early phase of diabetic management when there is likelihood of rapid shifts in blood sugar levels. Himsworth[6] states that transient myopia occurred as an initial symptom in 49% of 47 cases under 45 years of age, and in 23% of 53 cases over 45 years, an average of 34%. In studying the refraction of patients who were starting a course of diabetic management, Granström[4] found increased hyperopia in 57 of 80 previously untreated cases, and in only 7 of 38 who had had previous periods of diabetic treatment. The explanation of these changes probably lies, as suggested by Duke-Elder,[2] in the change in the index of refraction of the lens, due to the upset in osmotic balance between the chlorid content of the lens and that of the aqueous which occurs along with rapid shifts of the sugar and chlorid content of the blood. Waite and Beetham noted transient changes of refraction in only 6% of their patients, but this percentage was on the basis of history alone, since all their cases were not refracted under cycloplegia. They were able to demonstrate a weakness of accommodation in 40% of the 58 patients with transient hyperopia who were under 50 years of age, while in the entire group of diabetics, 21% showed demonstrable weakness of accommodation. Both these conditions tended to disappear under proper diabetic regimen.

Waite and Beetham made extensive slit-lamp studies of the cornea, iris and lens. The incidence of arcus senilis was the same in diabetics as in non-diabetics. Wrinkles in Descemet's membrane of the cornea

were found to increase with the age of the patient but were present in 26% of the diabetics as against 10% of the non-diabetics. In diabetics the wrinkles were found to appear earlier and to be more numerous in the individual eye. Among the diabetics, wrinkles were found in 60% of the gangrene cases, in 51% of the deep retinal hemorrhage cases, and in 43% of the diabetic neuritis cases.

Depigmentation of the iris was found in 6% of diabetics as compared with 2% of non-diabetics. This is probably due to a more facile release of pigment from the uveal tract of the diabetic as can be demonstrated by massaging the eye during slit-lamp examination or on opening the anterior chamber surgically. Correspondingly, pigment deposits were found on the posterior surface of the cornea in 11% of diabetics and in 5% of non-diabetics. A possible cause of this may be damage to the iris pigment epithelium through selective glycogen storage. Histologically, Waite and Beetham have been able to demonstrate "abnormal glycogen deposits in the retina and optic nerve, in the epithelium of the lens capsule, and especially in the pigment epithelium of iris and ciliary body, which may show an increase of many times its normal thickness due to glycogen alone."

It is of interest that among their 2002 diabetics, Waite and Beetham found 10 patients with Argyll-Robertson pupils, in 5 of whom no evidence for the diagnosis of syphilis could be elicited.

The results of Waite and Beetham's slit-lamp examinations of the lenses of diabetics and non-diabetics are of considerable interest in that, in patients over 20 years of age, opacities were found by the slit-lamp in 50% of diabetics and in 57% of non-diabetics. This would seem to refute the usual assumption that cataract occurs more frequently in diabetics. Among 297 juvenile diabetics, 11 patients with "flocculi" cataracts were found (4%). These are the supposedly typical diabetic cataracts but they seem to be indistinguishable from the cataracts of parathyroid tetany, scleroderma or myotonic dystrophy. In half of these patients, the diabetes was poorly controlled at the time of observation, but in the other half the opacities appeared and progressed in spite of most satisfactory control of the diabetes.

Carey and Hunt[1] report a study on the chemical nature of cataract in the diabetic in the course of which they analyzed for cholesterol, total calcium and total non-lipoid phosphorous 10 normal lenses, 13 cataractous lenses of diabetic patients (not the juvenile flocculi cataracts), and 30 cataractous lenses of non-diabetic individuals. They found that the normal lens contains approximately 400 mg. % cholesterol, 9.5 mg. % calcium, and 16.5 mg. % phosphorus. The cataractous lens contains 522 mg. % cholesterol (20% more than the normal lens), and 31.6 mg. % calcium (three times normal lens or blood). The cataractous lens of the non-diabetic contains 19.7 mg. % of phosphorus (slightly more than normal), but the cataractous lens of the diabetic contains 6.2 mg. % phosphorus (less than half the normal). They state: "The cataract forming in the eye of the diabetic appears chemically to be the classical senile cataract in all respects save one. The phosphorus metabolism is markedly different. What importance this has one does not know at present."

HENRY P. WAGENER, M.D.

REFERENCES.

1. Carey, H. U., and Hunt, H. M.: The Chemical Nature of Cataract in the Diabetic, New England J. Med., **212**, 463, 1935.
2. Duke-Elder, W. S.: Changes in Refraction in Diabetes Mellitus, Brit. J. Ophthal., **9**, 167, 1935.
3. Folk, M. L., and Soskin, S.: The Fundus Oculi in Diabetes Mellitus, Am. J. Ophthal., **18**, 432, 1935.
4. Granström, K. O.: Refraktionsveränderungen bei Diabetes mellitus, Acta ophth., **11**, 1, 1933.
5. Gray, W. A.: Ocular Conditions in Diabetes Mellitus, Brit. J. Ophth., **17**, 577, 1933.
6. Himsworth, H. P.: Temporary Visual Disturbance as an Initial Symptom of Diabetes Mellitus, Brit. Med. J., **2**, 1184, 1932.
7. Wagener, H. P., Dry, T. J., and Wilder, R. M.: Retinitis in Diabetes, New England J. Med., **211**, 1131, 1934.
8. Waite, J. H., and Beetham, W. P.: The Visual Mechanism in Diabetes Mellitus, Ibid, **212**, 367, 429, 1935.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 16, 1935

A Bloodless Method for Continuous Recording of the Peripheral Circulation and its Application in Physiology and Pharmacology.—Hans Molitor and Michael Kniazuk (Merck Institute of Therapeutic Research, Rahway, New Jersey). A bloodless method for studying of the peripheral vascular circulation is described, based on on the principle of simultaneous recording of surface temperature and light transmission through the skin. A rabbit's ear is placed between a steady source of light and a photocell. Vasodilation decreases the amount of light transmitted through the skin and consequently lowers the current output from the photocell; the opposite effect takes place during vasoconstriction. In order to differentiate between active hyperemia and passive congestion, the surface temperature of the area under observation is measured thermoelectrically. During active hyperemia the skin temperature is increased, while during passive congestion it remains either unchanged or is lowered. The current fluctuations produced by the photocell and the thermocouple are continuously recorded on a paper kymograph. The method is not only useful for the analysis of vasoconstricting or dilating drugs but can also be applied to the investigation of local and general anesthetics and sedatives, based on the observation that the ear vessels of the rabbit respond with vasoconstriction to almost any type of mechanical or sensory stimulus, whether applied to the ear or other parts of the body.

The Effect of Combination with Diazo Compounds on the Immunological Reactivity of Antibodies.—Harry Eagle, Dorothea E. Smith and Percy Vickers (Laboratory of Bacteriology, University of Pennsylvania). Sufficient coupling with diazo compounds eventually destroyed the reactivity of all the antisera here studied. This was due to the progressive and simultaneous decrease in the reactivity of all the anti-

body molecules, rather than the inactivation of an increasing proportion of molecules. The rate of inactivation varied considerably among the several antisera. By stopping the reaction at intervals, it was possible to prepare partially inactivated antisera of peculiarly modified reactivity.

Thus, the flocculating activity of diphtheria antitoxin with toxin was completely destroyed long before there was any demonstrable impairment of its protective titer *in vivo*. The first change induced in antipneumococcus horse sera was the complete loss of reactivity with the capsular carbohydrate at a time when the agglutinating, animal-protecting, and complement-fixing activities of the sera were only slightly affected. On further coupling, the sera no longer caused visible agglutination; but aggregation of the serum-treated bacteria could be induced by centrifugation. Still further coupling destroyed all antibody activity.

Rabbit antisera to egg albumin and horse serum no longer precipitated the homologous antigen after treatment with diazo compounds, due to their failure to combine with the antigen. The hemolytic, complement-fixing and lipoid-flocculating activities of coupled rabbit antisera to sheep red blood cells fell off in parallel; the hemagglutinin seemed somewhat more resistant. The reagin of syphilitic serum was destroyed almost instantaneously by comparatively small amounts of diazo compounds. Finally, in the case of antityphoid agglutinin, the isoelectric point of the coupled antibody, measured on the surface of specifically sensitized bacteria, was found to shift from an original value of pH 4.7 to one of less than pH 2.7 as progressively more sulfanilic acid radicals added on to the antibody molecule.

The groups in protein which participate in its reaction with diazo compounds probably include aliphatic amines, the imidazole ring of histidine, the indole group of tryptophane, the NH of proline and hydroxyproline, and the phenolic group of tyrosine. The properties of the coupled antibody suggest the extent to which these groups participate in the combination of antibody with antigen, and the extent also to which they may be responsible for the characteristic properties of the antigen-antibody compounds.

The Behavior of Polymorphonuclear Leukocytes Outside the Bloodvessels.—E. R. Clark and E. L. Clark (Laboratory of Anatomy, University of Pennsylvania). Polymorphonuclear leukocytes were studied microscopically in the living animal, in the transparent tails of Amphibia and in transparent chambers installed in rabbits' ears, where they were observed in circulating vessels, in the act of migrating through vessel walls, in the outside tissue and in the interior of blocked lymphatics.

The process of emigration of individual leukocytes from bloodvessels was the same in Amphibia and mammal. Polymorphs which emigrated following endothelial changes, in the absence of any localized focus of attraction in the tissue, moved around rapidly at random for the first 24 hours, after which they became more sluggish and finally, after 4 to 6 days, rounded up and remained motionless. In the rabbit, phagocytosis of such rounded cells by macrophages was observed.

In microinflammations produced by injecting dilute croton oil into tadpoles' tails, polymorphs observed continuously in the living were seen to migrate toward the croton oil, to become stationary at a short

distance from it, to lose their granulation and send out fine processes, while still retaining their polymorphic nuclei. In specimens fixed and stained at this stage, 95% of the leukocytes in the inflammation area, exclusive of macrophages, were polymorphonuclear. Following extrusion of the oil, the polymorphs, after temporarily resuming their amœboid form, again became stationary in a rounded form. In specimens fixed in this later stage (24 to 48 hours), counts of leukocytes, exclusive of macrophages, showed 75% to be mononuclears. Disintegration of leukocytes was limited to a few cells. Observation of all the connective-tissue cells and endothelial nuclei of the entire area of inflamation over periods of 40 hours excluded the possibility of the transformation of such cells into any form of leukocyte and continuous observation of all the surrounding bloodvessels failed to show any secondary emigration from the blood stream. Furthermore, in a number of experiments individual polymorphs were watched continuously and the rounding up of these cells and the subsequent coalescence of their nuclear material into a mononuclear form was followed with camera lucida records.

In the rabbit, some polymorphs were observed to enter blocked lymphatics following emigration from a nearby vein, where they frequently remained corralled in the bulbous end of a lymphatic for weeks with no subsequent emigration of fresh leukocytes from the blood stream. When the same group of imprisoned cells was followed from day to day, the leukocytes which were at first easily identifiable as polymorphs, gradually assumed a rounded form with round nuclei, lost their granulations, and became smaller. When such specimens were fixed and stained the cellular contents of such a blocked lymphatic had the picture of a "round-cell infiltration."

The changes observed in polymorphs, which remained for some time outside the blood stream, into round mononuclear cells was evidently a simulation of, rather than a true transformation into, monocytes or lymphocytes, since the behavior of such changed leukocytes and the fact that they were frequently phagocytized by macrophages showed them to be partially degenerated cells. However, the strong resemblance of collections of leukocytes, known from their past history in the living animal to have been typical polymorphs which emigrated from the blood streams, to the mononuclear exudates and round cell infiltrations of pathologic material, suggests the possibility that the latter may be, in part at least, composed of changed polymorphs.

It is obvious that the conditions found outside the blood capillary, whether in the intercellular substance or in the interior of lymphatic vessels, furnish an environment which is unhealthy for the polymorphs. In their behavior here they contrast markedly with true monocytes, which thrive in the tissue spaces. We have seen them to continue, as macrophages, to manifest sporadic amœboid activity and capacity for phagocytosis for months.

Evaluation of Mercurial Antiseptics in the Presence of Serum.—Dorothea E. Smith, E. J. Czarnetzky and Stuart Mudd (Laboratory of Bacteriology, University of Pennsylvania). Several mercurial antiseptics have been compared for their germicidal action in saline and in 80% serum. An accurate method of plating has been used, and the

time and concentration required for 50% killing of a culture of smooth *B. typhosus* has been taken as a basis of comparison.

Metaphen, merthiolate, mercurochrome and bichlorid of mercury all combine with serum proteins. When maximum combination is secured the resulting compounds possess no antiseptic action. The mercury content found by analysis of the equilibrium germicide-protein compound is the same, within the limits of experimental error, for all four germicides. Equilibrium has been approached in both directions. In one case an excess of mercurial was used, and in the other an excess of serum proteins. In the latter case, the rate of combination was determined by adding the calculated amount of mercurial and noting the time when the mixture no longer possessed antiseptic action. The ratio of the rate with which the mercury of the mercurials combines with bacteria and with serum proteins is more favorable in the case of some of the mercurials than with the others. These compounds kill bacteria, then, only in proportion to their mercury content. The decrease in germicidal activity when used in serum is equal to the amount of mercury chemically combined with serum. When used in saline, the killing power of the antiseptics is directly proportional to their concentration, but when used in serum, the killing power is proportional only to the concentration of antiseptics not combined with the serum proteins. It has been found that approximately 0.4 gm. as mercury of any of these mercurials can be bound by one liter of normal horse serum.

It follows that the effect of serum is such that neither metaphen, merthiolate, mercurochrome, nor bichlorid of mercury may be used as intravenous antiseptics.

ERRATUM.

The footnote referring to Dr. Rawls' article on agranulocytosis (p. 131, January issue of this JOURNAL) should read: "In a more recent communication, now in press, Rawls stresses the infrequency of agranulocytosis in a large series of amidopyrin cases."

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the articles and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers). Titles can be included for less than 25 references.

Return postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Two hundred and fifty reprints, with covers, are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the JOURNAL, will be translated at its expense.